FUSED HETEROCYCLIC DERIVATIVES AND METHODS OF USE

FIELD OF THE INVENTION

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer.

BACKGROUND OF THE INVENTION

Protein kinases represent a large family of proteins, which play a central role in the regulation of a wide variety of cellular processes, maintaining control over cellular function. A partial list of such kinases includes abl, Akt, bcr-abl, Blk, Brk, Btk, c-kit, c-Met, c-src, c-fms, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes, and Zap70. Inhibition of such kinases has become an important therapeutic target.

The hepatocyte growth factor receptor ("c-Met") is a unique receptor tyrosine kinase shown to be overexpressed in a variety of malignancies. c-Met typically comprises, in its native form, a 190-kDa heterodimeric (a disulfide-linked 50-kDa α-chain and a 145-kDa β-chain) membrane-spanning tyrosine kinase protein (Proc. Natl. Acad. Sci. USA, 84:6379-6383 (1987)). c-Met is mainly expressed in epithelial cells and stimulation of c-Met leads to scattering, angiogenesis, proliferation and metastasis. (See Cytokine and Growth Factor Reviews, 13:41-59 (2002)).

The ligand for c-Met is hepatocyte growth factor (also known as scatter factor, HGF and SF). HGF is a heterodimeric protein secreted by cells of mesodermal origin (Nature, 327:239-242 (1987); J. Cell Biol., 111:2097-2108 (1990)).

Various biological activities have been described for HGF through interaction with c-met (Hepatocyte Growth Factor- Scatter Factor (HGF-SF) and the c-Met Receptor, Goldberg and Rosen, eds., Birkhauser Verlag-Basel, 67-79 (1993). The biological effect of HGF/SF may depend in part on the target cell. HGF induces a spectrum of biological activities in epithelial cells, including mitogenesis, stimulation of cell motility and promotion of matrix invasion (Biochem. Biophys. Res. Comm., 122:1450-1459 (1984); Proc. Natl. Acad. Sci. U.S.A., 88:415-419 (1991)). It stimulates the motility and invasiveness of carcinoma cells, the former having been implicated in the migration of cells required for metastasis. HGF can also act as a "scatter factor", an activity that promotes the dissociation of epithelial and vascular endothelial

cells (Nature, 327:239-242 (1987); J. Cell Biol., 111:2097-2108 (1990); EMBO J., 10:2867-2878 (1991); Proc. Natl. Acad. Sci. USA, 90:649-653 (1993)). Therefore, HGF is thought to be important in tumor invasion (Hepatocyte Growth Factor-Scatter Factor (HGF-SF) and the C-Met Receptor, Goldberg and Rosen, eds., Birkhauser Verlag-Basel, 131-165 (1993)).

HGF and c-Met are expressed at abnormally high levels in a large variety of solid tumors. High levels of HGF and/or c-Met have been observed in liver, breast, pancreas, lung, kidney, bladder, ovary, brain, prostate, gallbladder and myeloma tumors in addition to many others. The role of HGF/c-Met in metastasis has been investigated in mice using cell lines transformed with HGF/c-Met (J. Mol. Med., 74:505-513 (1996)). Overexpression of the c-Met oncogene has also been suggested to play a role in the pathogenesis and progression of thyroid tumors derived from follicular epithelium (Oncogene, 7:2549-2553 (1992)). HGF is a morphogen (Development, 110:1271-1284 (1990); Cell, 66:697-711 (1991)) and a potent angiogenic factor (J. Cell Biol., 119:629-641 (1992)).

Recent work on the relationship between inhibition of angiogenesis and the suppression or reversion of tumor progression shows great promise in the treatment of cancer (Nature, 390:404-407 (1997)), especially the use of multiple angiogenesis inhibitors compared to the effect of a single inhibitor. Angiogenesis can be stimulated by HGF, as well as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

Angiogenesis, the process of sprouting new blood vessels from existing vasculature and arteriogenesis, the remodeling of small vessels into larger conduit vessels are both physiologically important aspects of vascular growth in adult tissues. These processes of vascular growth are required for beneficial processes such as tissue repair, wound healing, recovery from tissue ischemia and menstrual cycling. They are also required for the development of pathological conditions such as the growth of neoplasias, diabetic retinopathy, rheumatoid arthritis, psoriasis, certain forms of macular degeneration, and certain inflammatory pathologies. The inhibition of vascular growth in these contexts has also shown beneficial effects in preclinical animal models. For example, inhibition of angiogenesis by blocking vascular endothelial growth factor or its receptor has resulted in inhibition of tumor growth and in retinopathy. Also, the development of pathological pannus tissue in rheumatoid arthritis involves angiogenesis and might be blocked by inhibitors of angiogenesis.

The ability to stimulate vascular growth has potential utility for treatment of ischemia-induced pathologies such as myocardial infarction, coronary artery disease, peripheral vascular disease, and stroke. The sprouting of new vessels and/or the expansion of small vessels in ischemic tissues prevents ischemic tissue death and induces tissue repair. Certain diseases are

known to be associated with deregulated angiogenesis, for example ocular neovascularization, such as retinopathies (including diabetic retinopathy), age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, inflammatory disease, such as a rheumatoid or rheumatic inflammatory disease, especially arthritis (including rheumatoid arthritis), or other chronic inflammatory disorders, such as chronic asthma, arterial or post-transplantational atherosclerosis, endometriosis, and neoplastic diseases, for example so-called solid tumors and liquid tumors (such as leukemias). Treatment of malaria and related viral diseases may also be mediated by HGF and cMet.

Elevated levels of HGF and c-Met have also been observed in non-oncological settings, such as hypertension, myocardial infarction and rheumatoid arthritis. It has been observed that levels of HGF increase in the plasma of patients with hepatic failure (Gohda et al., supra) and in the plasma (Hepatol., 13:734-750 (1991)) or serum (J. Biochem., 109:8-13 (1991)) of animals with experimentally induced liver damage. HGF has also been shown to be a mitogen for certain cell types, including melanocytes, renal tubular cells, keratinocytes, certain endothelial cells and cells of epithelial origin (Biochem. Biophys. Res. Commun., 176:45-51 (1991); Biochem. Biophys. Res. Commun., 174:831-838 (1991); Biochem., 30:9768-9780 (1991); Proc. Natl. Acad. Sci. USA, 88:415-419 (1991)). Both HGF and the c-Met proto-oncogene have been postulated to play a role in microglial reactions to CNS injuries (Oncogene, 8:219-222 (1993)).

Metastatic SCC cells overexpress c-Met and have enhanced tumoregenesis and metastasis in vivo [G. Gong et al., Oncogene, 23:6199-6208 (2004)]. C-Met is required for tumor cell survival [N. Shinomiya et al., Cancer Research, 64:7962-7970 (2004)]. For a general review see C. Birchmeier et al., Nature Reviews/Molecular Biology 4:915-925 (2003).

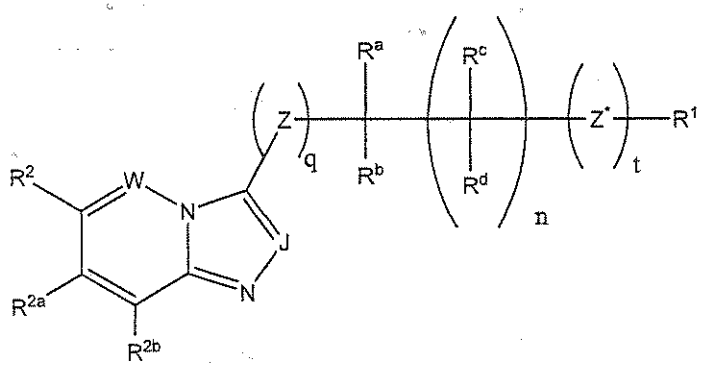
In view of the role of HGF and/or c-Met in potentiating or promoting such diseases or pathological conditions, it would be useful to have a means of substantially reducing or inhibiting one or more of the biological effects of HGF and its receptor. Thus a compound that reduces the effect of HGF would be a useful compound. Compounds of the current invention have not been previously described as inhibitors of angiogenesis such as for the treatment of cancer.

Sugen application WO 05/010005 describes certain Triazolotriazine compounds that are c-met inhibitors. Diamon Shamrock Corp. application WO 83/00864 discloses certain Triazolotriazine compounds that are useful as anti-inflammatory agents. Yamanouchi applications EP 1481955 and US 2005/0261297 disclose certain nitrogen-containing heterocyclic compounds that are therapeutic agents having a bone formation-stimulating effect.

Compounds of the current invention are inhibitors of c-Met.

SUMMARY OF THE INVENTION

In one aspect, there is provided a compound of formula I



I

wherein

J is N or CR^3;

W is CR^{2b};

Z and Z* are independently -O-, $-S(O)_v-$, or $-NR^5-$;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

R^1 is aryl, heteroaryl or heterocyclo any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^2 is

(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

R^{2a}, R^{2b} and R^3 are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} at each occurrence is independently, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$,

-(alkylene)$_m$-OC(=O)NR^{5}R^{5a}, -(alkylene)$_m$-OC(=S)NR^{5}R^{5a}, -(alkylene)$_m$-SO$_2$NR^{5}R^{5a},
-(alkylene)$_m$-N(R^5)SO$_2$R^4, -(alkylene)$_m$-N(R^5)SO$_2$NR^{5}R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or
-(alkylene)$_m$-N(R^5)SO$_2$R^4;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^4,
-(alkylene)$_m$-S(O)$_v$R^4, -(alkylene)$_m$-NR^{5}R^{5a}, -(alkylene)$_m$-C(=O)R^4,
-(alkylene)$_m$-C(=S)R^4, -(alkylene)$_m$-C(=O)OR^4, -(alkylene)$_m$-OC(=O)R^4,
-(alkylene)$_m$-C(=S)OR^4, —(alkylene)$_m$-C(=O)NR^{5}R^{5a}, -(alkylene)$_m$-C(=S)NR^{5}R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=S)NR^{5}R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)R^4, -(alkylene)$_m$-N(R^5)C(=S)R^4,
-(alkylene)$_m$-OC(=O)NR^{5}R^{5a}, -(alkylene)$_m$-OC(=S)NR^{5}R^{5a}, -(alkylene)$_m$-SO$_2$NR^{5}R^{5a},
-(alkylene)$_m$-N(R^5)SO$_2$R^4, -(alkylene)$_m$-N(R^5)SO$_2$NR^{5}R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or
-(alkylene)$_m$-N(R^5)SO$_2$R^4;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

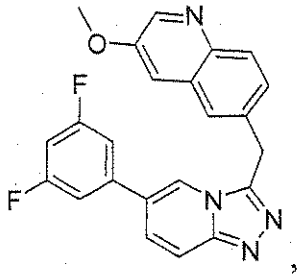
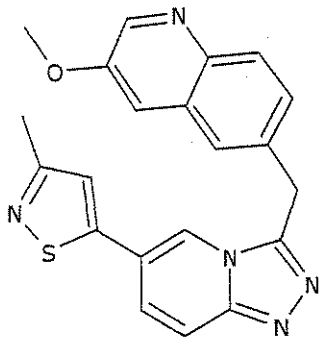
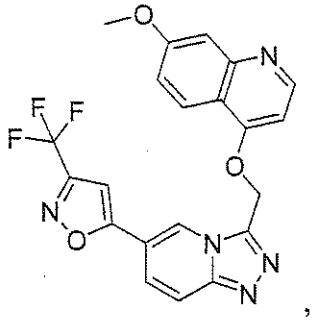
m is 0 or 1;

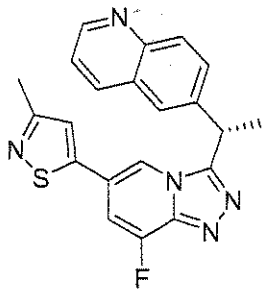
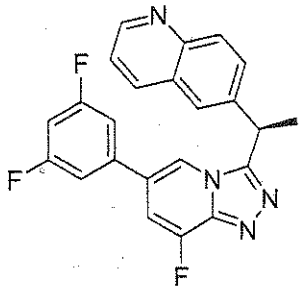
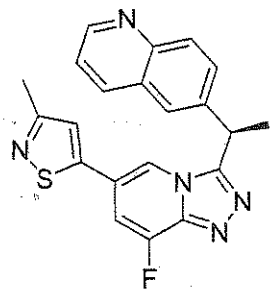
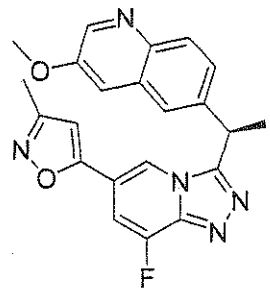
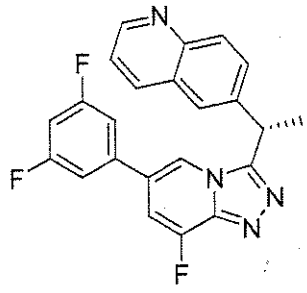
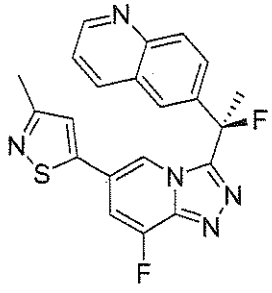
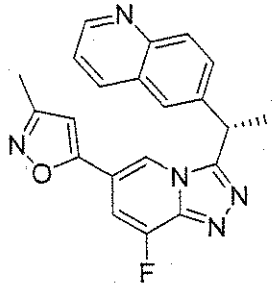
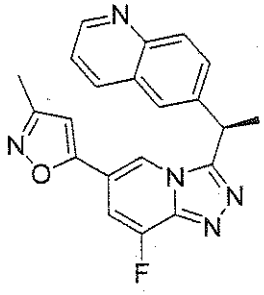
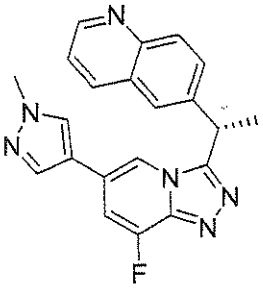
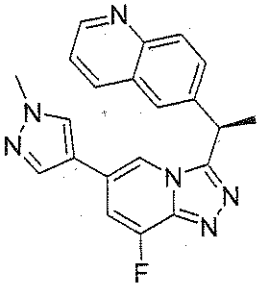
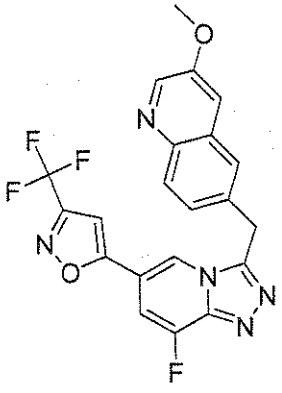
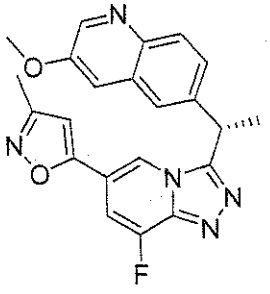
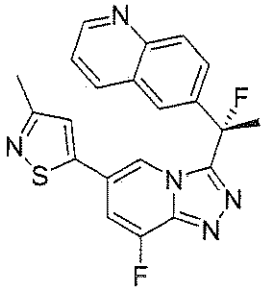
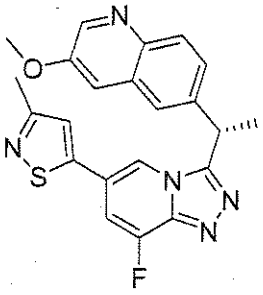
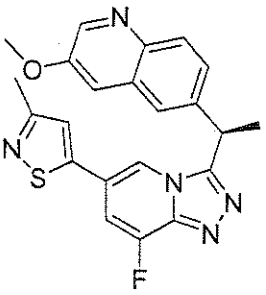
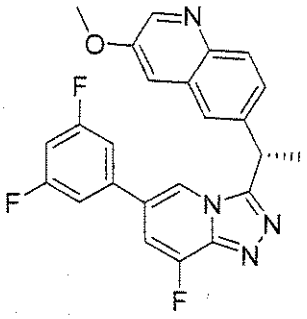
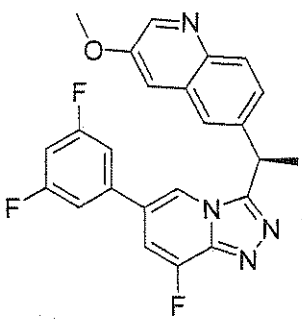
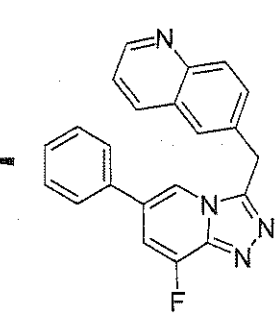
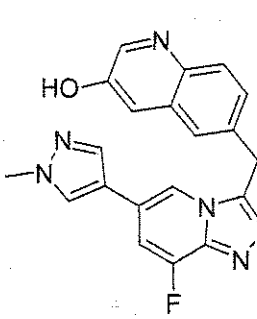
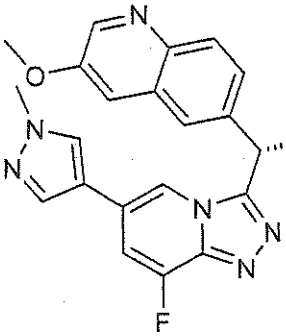
n is 0, 1 or 2;

q and t are each independently 0 or 1;

v is 0, 1 or 2;

wherein said compound is selected from


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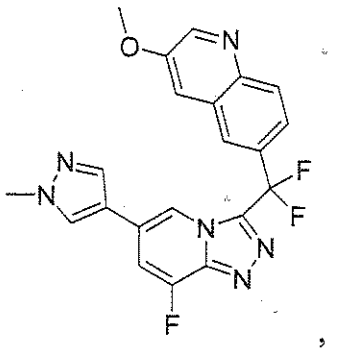
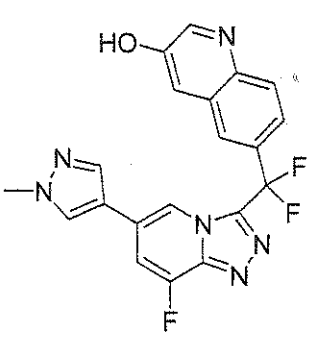
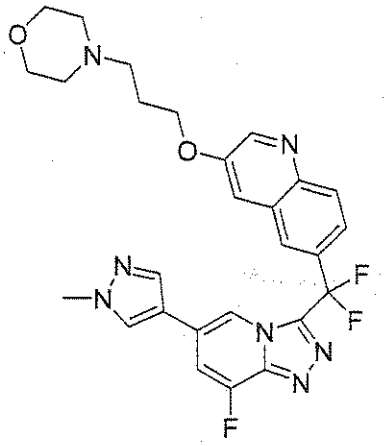
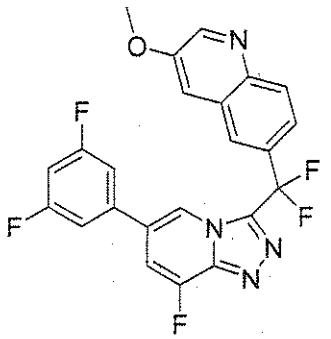
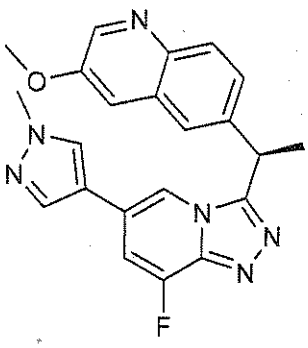
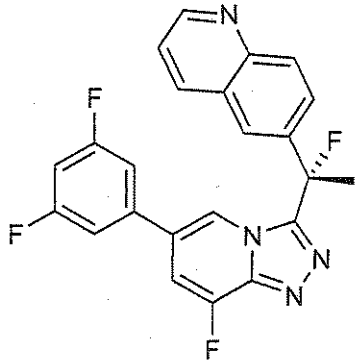
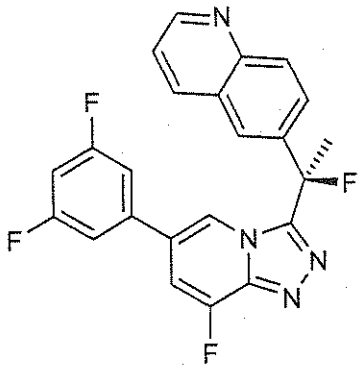
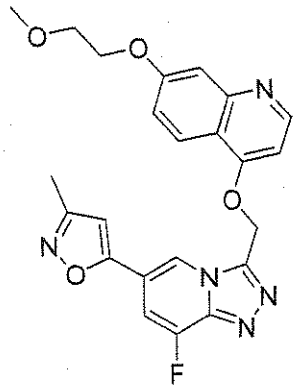
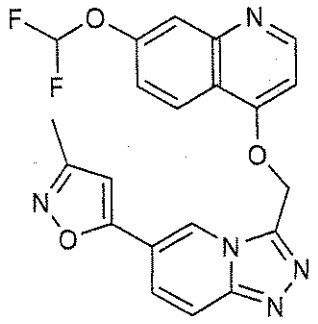
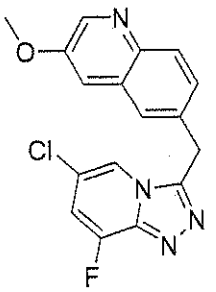
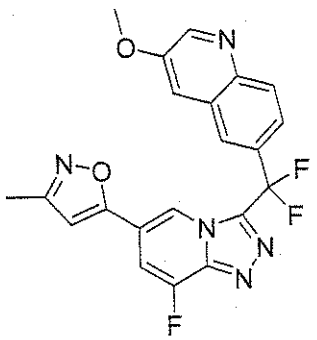
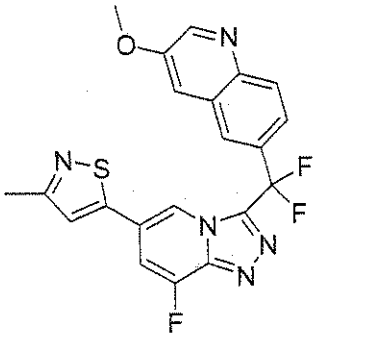

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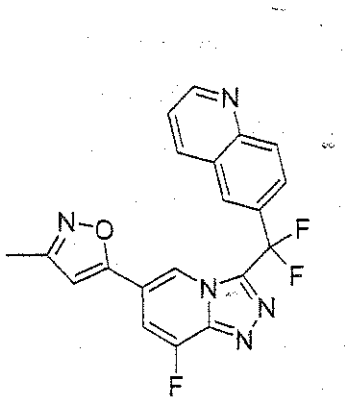
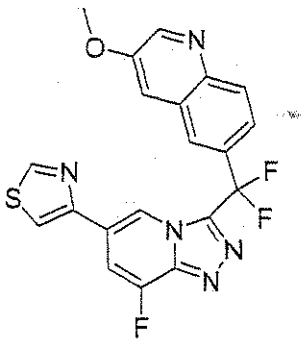
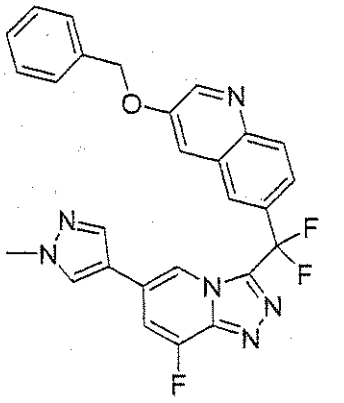
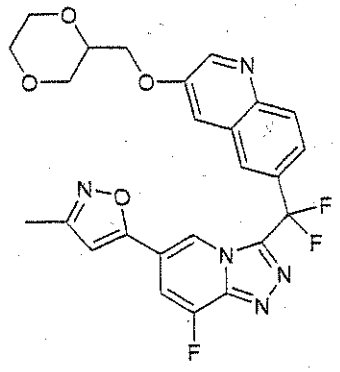
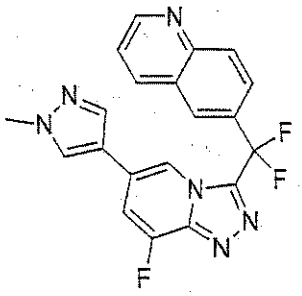
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and salts thereof.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above together with a pharmaceutically acceptable vehicle or carrier.

In another aspect, there is provided a compound as defined above for treating cancer in a subject.

In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for treating cancer in a subject.

In another aspect, there is provided a compound as defined above for reducing tumor size in a subject.

In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for reducing tumor size in a subject.

In another aspect, there is provided a compound as defined above for treating HGF mediated disorders in a subject.

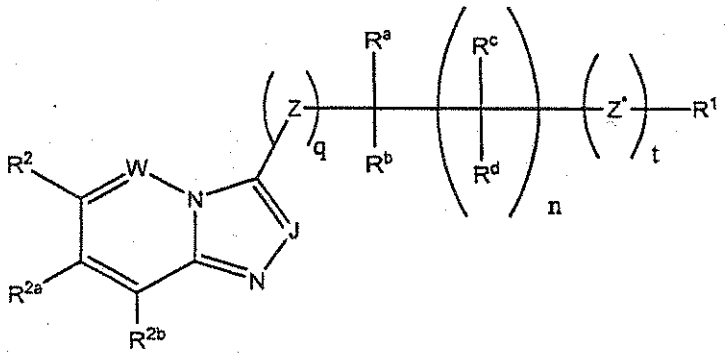
In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for treating HGF mediated disorders in a subject.

In another aspect, there is provided a compound as defined above for reducing metastasis in a tumor in a subject.

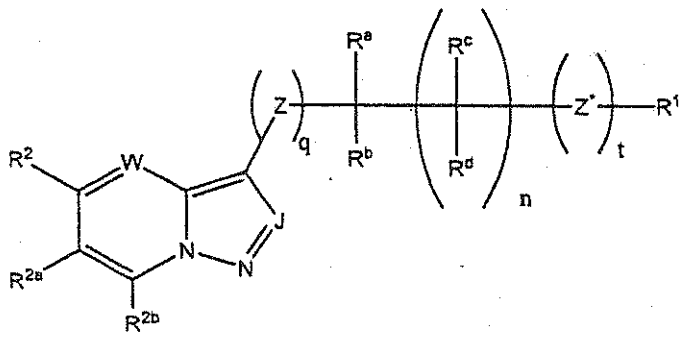
In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for reducing metastasis in a tumor in a subject.

DESCRIPTION OF THE INVENTION

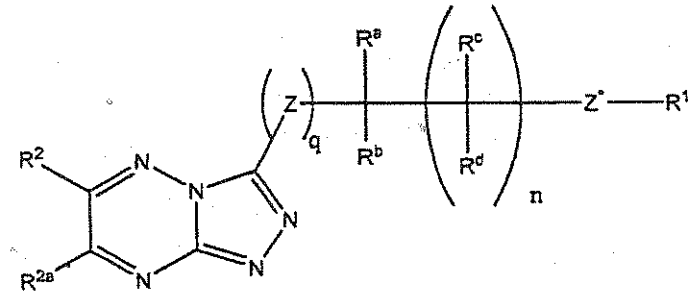
A class of compounds useful in treating cancer and angiogenesis is defined by Formulae I, II, III, IV, V, VI and VII



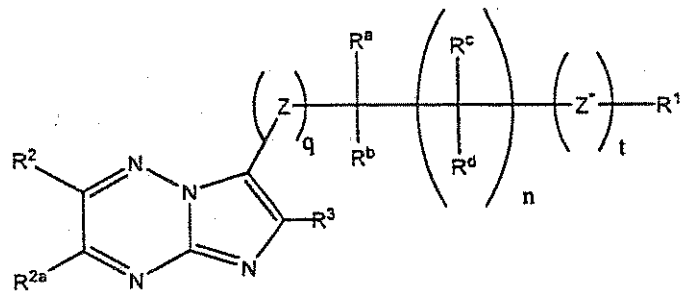
I



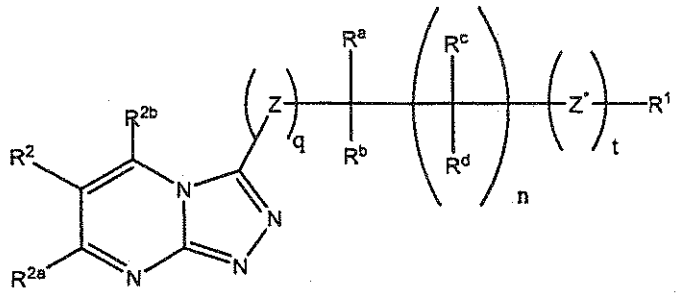
II



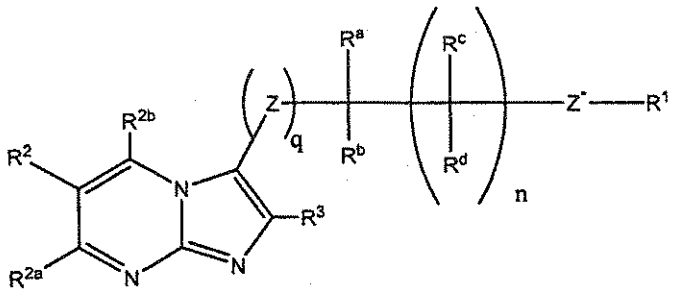
III



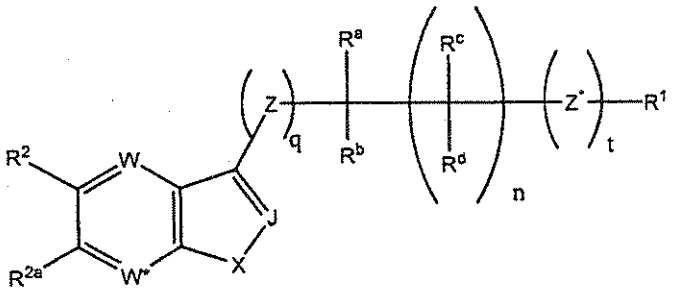
IV



V



VI



VII

enantiomers, diastereomers, salts and solvates thereof wherein

J is N or CR^3;

W is CR^{2b};

W* is N or CR^{2b};

X is O or S;

Z and Z* are independently -O-, $-S(O)_v-$, or $-NR^5-$;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

R^1 is aryl, heteroaryl or heterocyclo any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^2 is

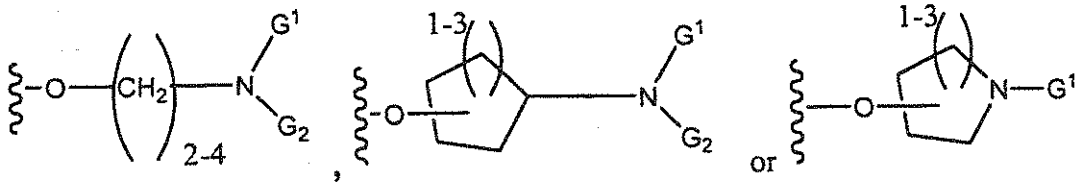
(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

provided that in compounds of formula I when W and J are both N, R^2 is other than

(a) $-NR^5R^{5a}$ where R^5 and R^{5a} are independently H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl; and

(b) phenyl substituted with a group



where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring;

R^{2a}, R^{2b} and R^3 are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl,

arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$,

-(alkylene)$_m$-N(R^5)C(=O)NR^5R^{5a}, -(alkylene)$_m$-N(R^5)C(=S)NR^5R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)R^4, -(alkylene)$_m$-N(R^5)C(=S)R^4,
-(alkylene)$_m$-OC(=O)NR^5R^{5a}, -(alkylene)$_m$-OC(=S)NR^5R^{5a}, -(alkylene)$_m$-SO_2NR^5R^{5a},
-(alkylene)$_m$-N(R^5)SO_2R^4, -(alkylene)$_m$-N(R^5)SO_2NR^5R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or
-(alkylene)$_m$-N(R^5)SO_2R^4;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

m is 0 or 1;

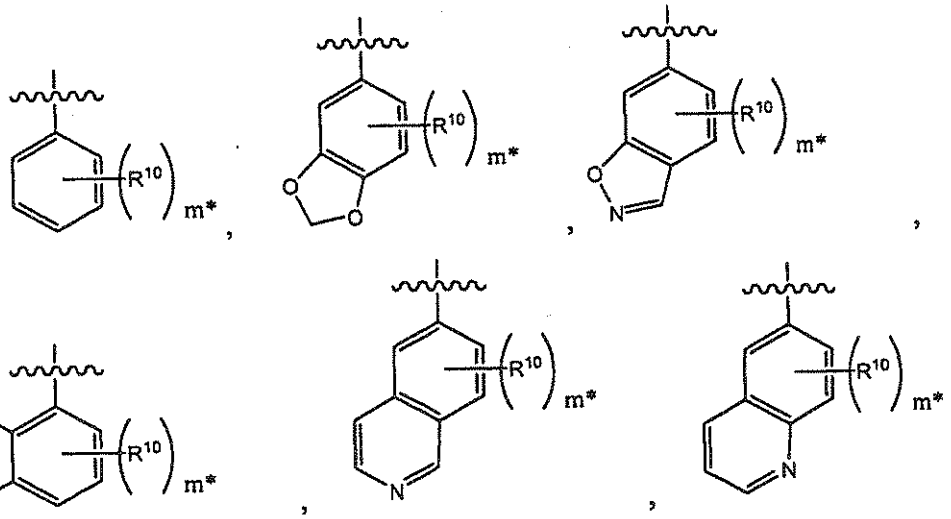
n is 0, 1 or 2;

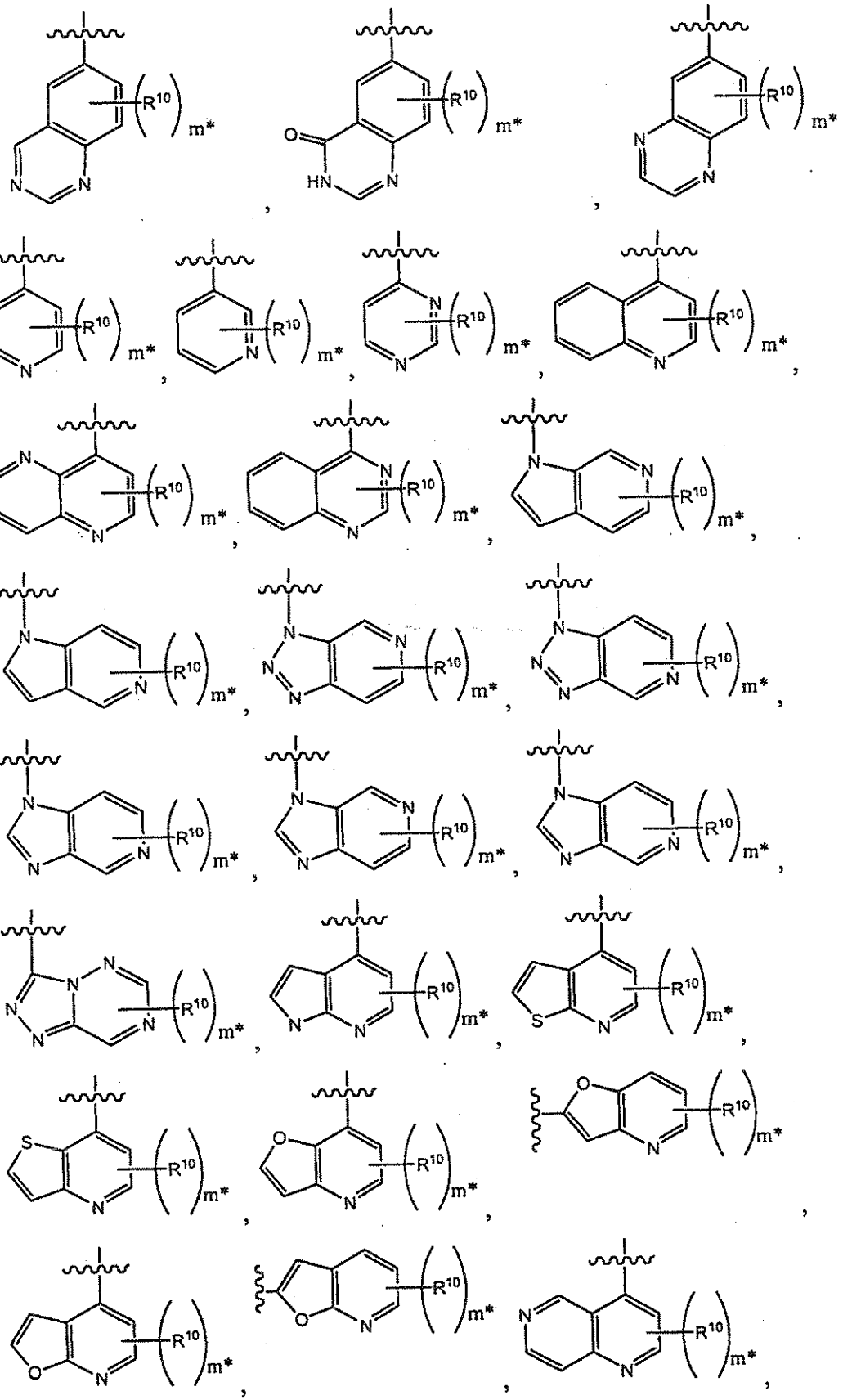
q and t are each independently 0 or 1;

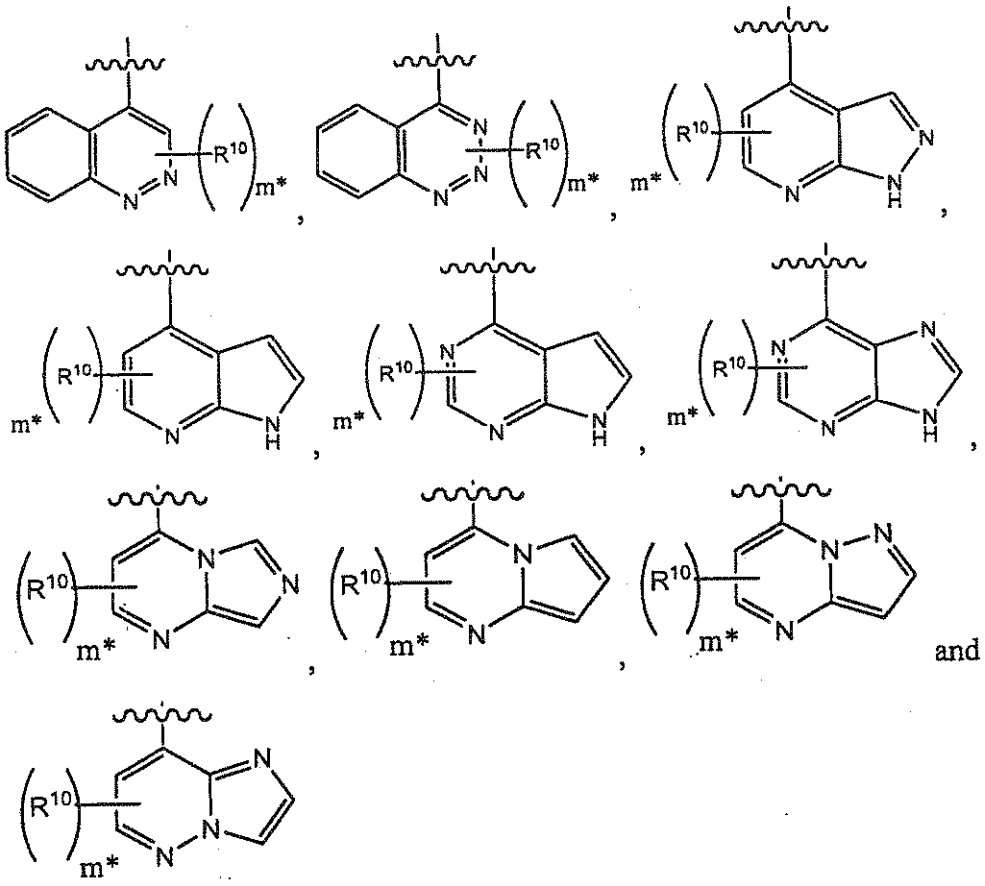
v is 0, 1 or 2.

Preferred compounds include compounds wherein R^1 is phenyl, naphthyl, benzodioxolyl, benzooxazolyl, benzoisoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrimidinyl, pyrazidinyl, isoquinolinyl, quinolinyl, quinazolinyl, quinazolinonyl, quinoxalinyl, naphthyridinyl, benzotriazinyl, triazolopyridinyl, triazolopyrimidinyl, triazolopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazopyridazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, cinnolinyl, thienopyridinyl, thienopyrimidinyl, thienopyridazinyl, furopyridinyl, furopyrimidinyl, furopyrazidinyl, benzofuranyl, benzoimidazolyl, indolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, pyridopyrimidinyl, oxazolopyridinyl, thiazolopyridinyl, pyrazolopyrazinyl, triazolopyrazinyl and triazolopyridinyl any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance.

Preferred R^1 groups include

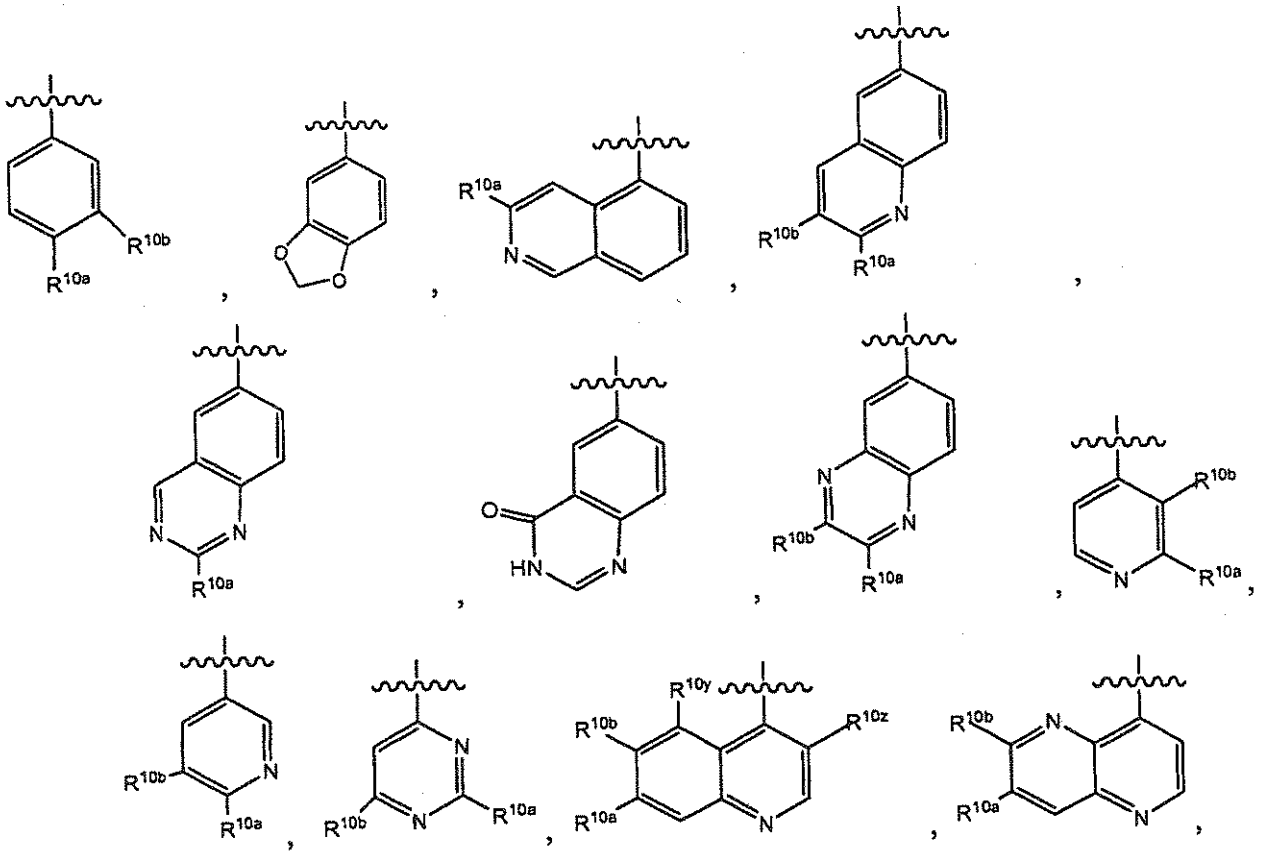


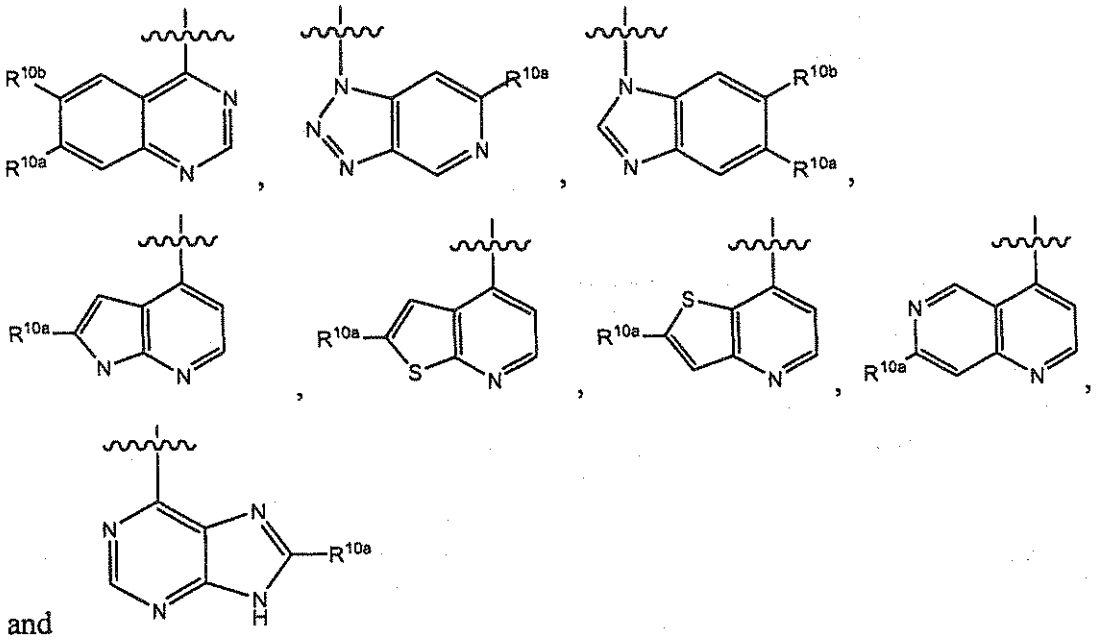




where m* is 0, 1, 2, 3, 4, 5 or 6, as allowed by valence.

Especially preferred R^1 groups include

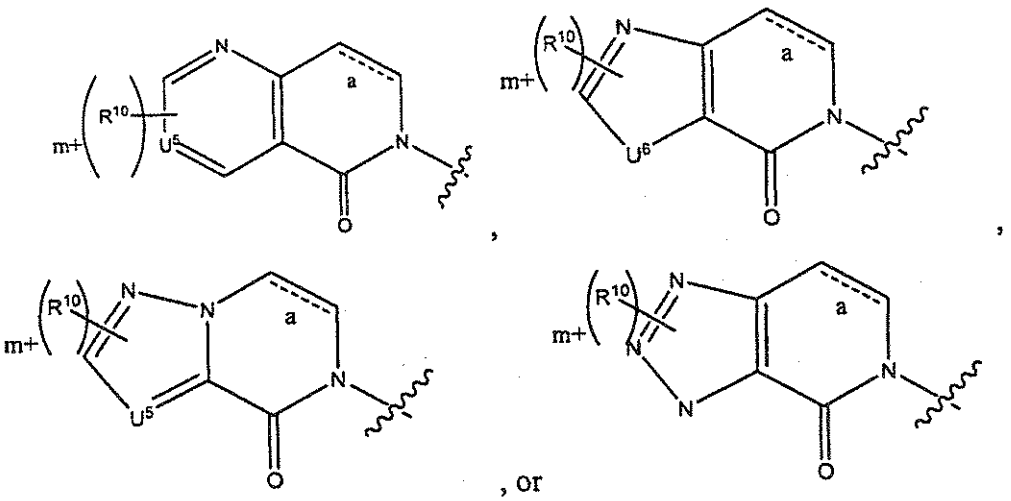




where R^{10a}, R^{10b}. R^{10y} and R^{10z} are independently absent, halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, -(alkylene)$_m$-OR^4, -(alkylene)$_m$-NR^5R^{5a}, -(alkylene)$_m$-$C(=O)R^4$, -(alkylene)$_m$-$C(=O)OR^4$, -(alkylene)$_m$-$OC(=O)R^4$, —(alkylene)$_m$-$C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)R^4$, -(alkylene)$_m$-$OC(=O)NR^5R^{5a}$, or -(alkylene)$_m$-$N(R^5)C(=O)OR^4$;

or where R^{10a} and R^{10b} combine to form an optionally substituted 3- to 8-membered ring system.

Preferred R^1 groups further include



wherein a is a bond or is absent;

U^5 is C or N;

U^6 is NH, O or S; and

m+ is 0, 1, 2 or 3 .

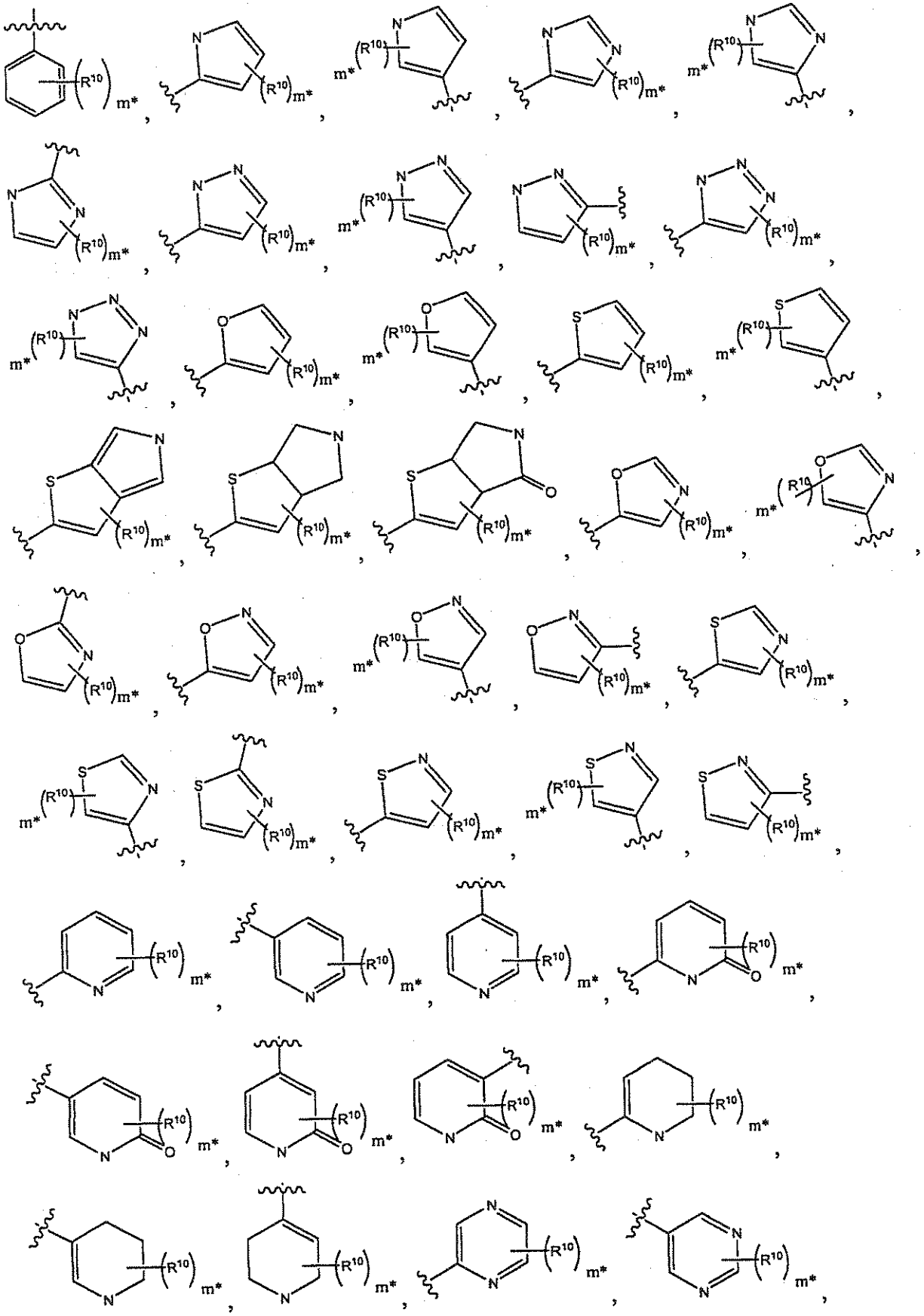
Most preferred R^1 groups include moieties that are either unsubstituted or independently substituted as allowed by valance with one or more halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, -(alkylene)$_m$-OR^4, -(alkylene)$_m$-NR^5R^{5a}, -(alkylene)$_m$-$C(=O)R^4$, -(alkylene)$_m$-$C(=O)OR^4$, -(alkylene)$_m$-$OC(=O)R^4$, -(alkylene)$_m$-$C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)R^4$, -(alkylene)$_m$-$OC(=O)NR^5R^{5a}$, or -(alkylene)$_m$-$N(R^5)C(=O)OR^4$.

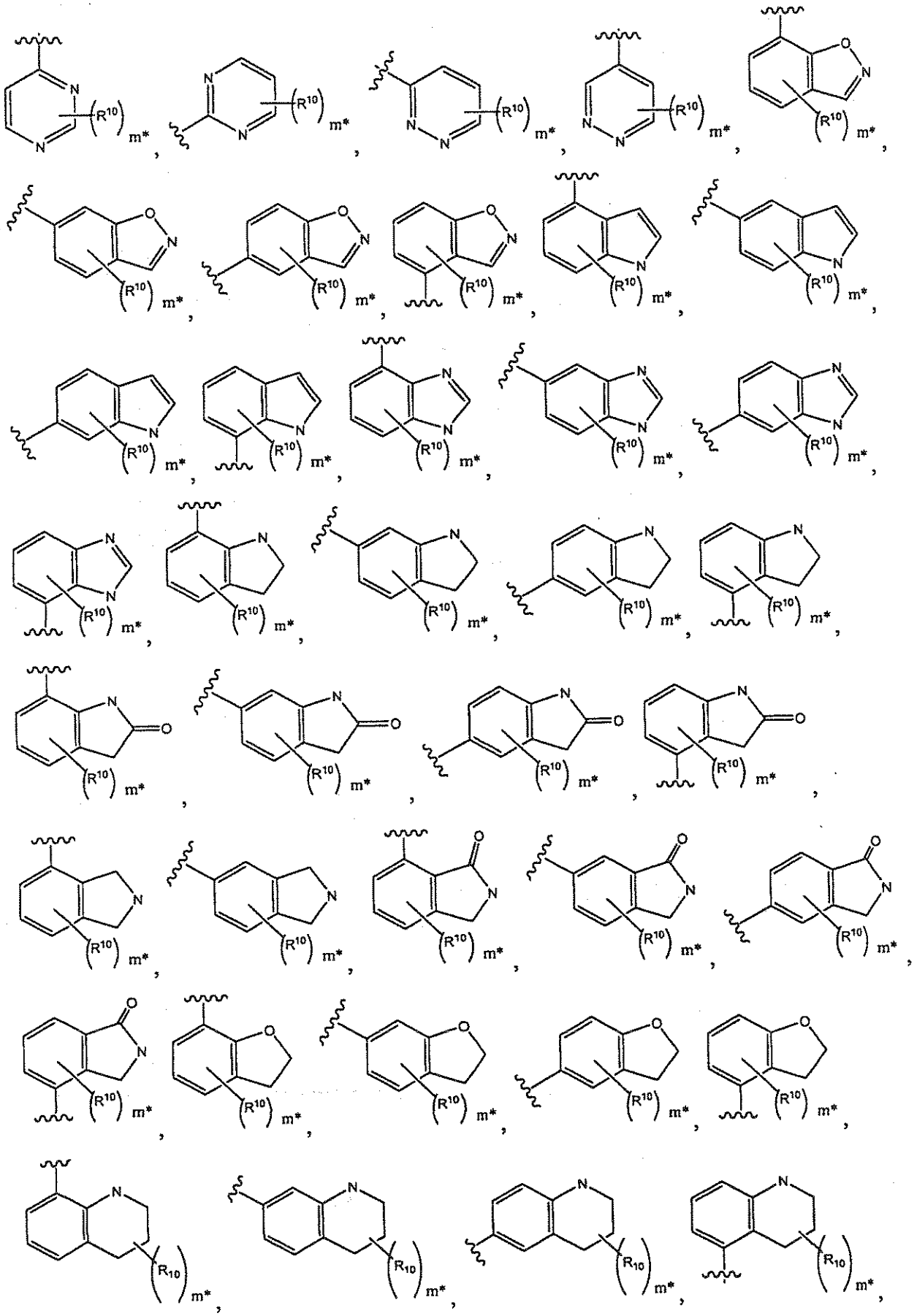
Preferred compounds of the present invention further include compounds wherein R^2 is H, halo, cyano, alkynyl, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=O)OR^4$, phenyl, naphthyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, tetrahydropyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, indolinonyl, isoidolinyl, isoindolinonyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, benzofuranyl, isobenzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, quinazolinonyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, quinoxalinyl, tetrahydroquinoxalinyl, benzomorpholinyl, dihydrobenzodioxinyl, imidazopyridinyl, naphthyridinyl, benzotriazinyl, triazolopyridinyl, triazolopyrimidinyl, triazolopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazopyridazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, cinnolinyl, thienopyrrolyl, tetrahydrothienopyrrolyl, dihydrothienopyrrolonyl, thienopyridinyl, thienopyrimidinyl, thienopyridazinyl, furopyridinyl, furopyrimidinyl, furopyrazidinyl, benzofuranyl, benzoimidazolyl, benzoisoxazolyl, benzothiazolyl, or benzoisothiazolyl any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance.

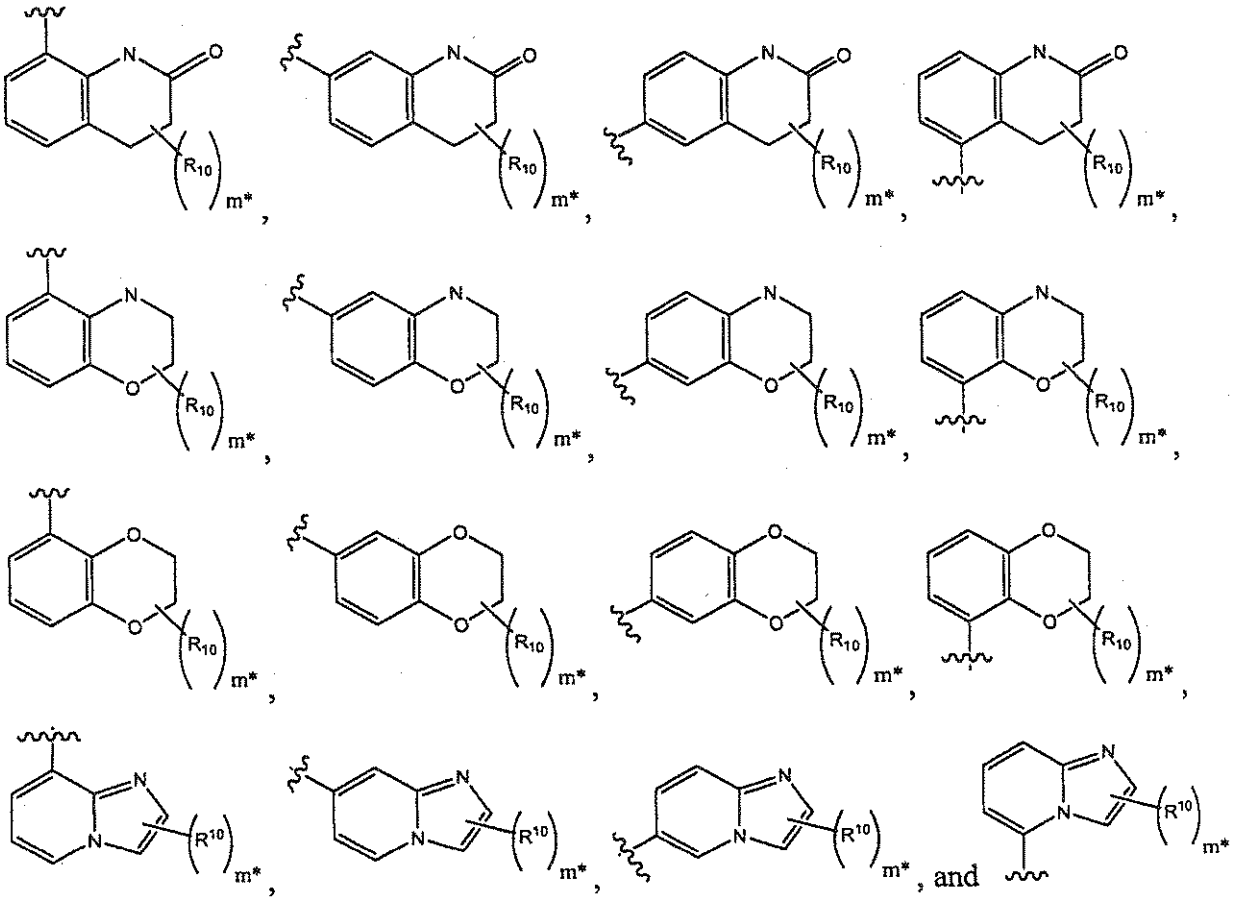
Preferred R^2 groups include

(a) halo, alkynyl, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$ or $-N(R^5)C(=O)OR^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance; and

(b) an aryl, heteroaryl or heterocyclo ring system selected from





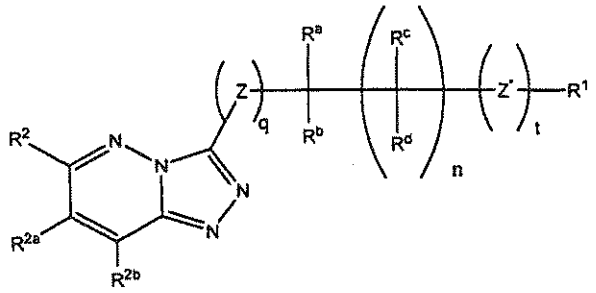


where m* is 0, 1, 2, 3, 4, 5 or 6, as allowed by valence.

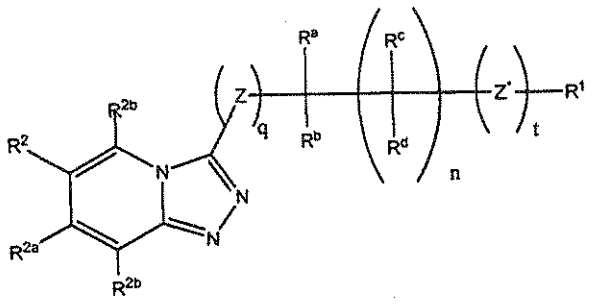
Preferred compounds of the present invention include compounds having either or both of preferred R^1 groups and preferred R^2 groups either alone or in any combination thereof..

Preferred compounds of the present invention include compounds wherein R^a, R^b, R^c and R^d groups are independently hydrogen, alkyl (especially methyl), and halogen (especially fluorine).

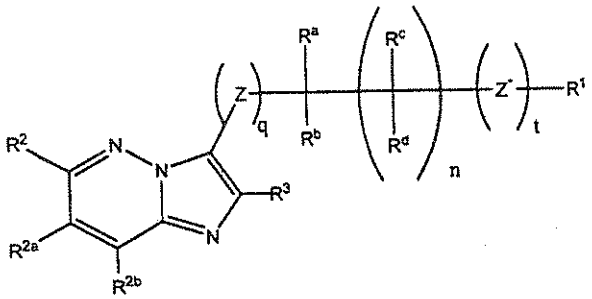
Preferred compounds within the scope of formula I and II include compounds of the following formualae IA, IB, IC, ID and IIA



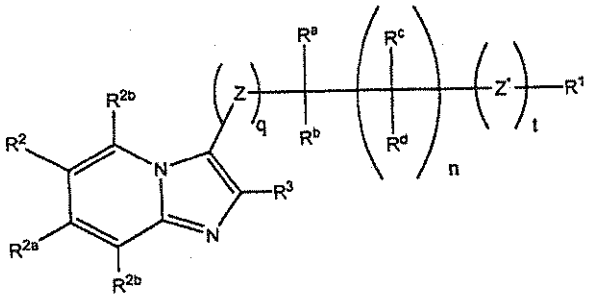
IA



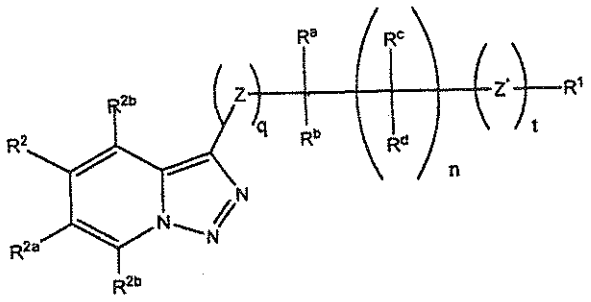
IB



IC



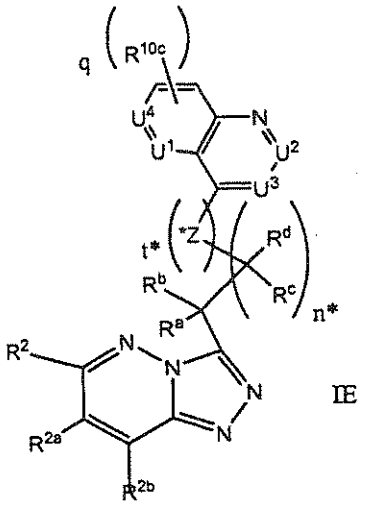
ID



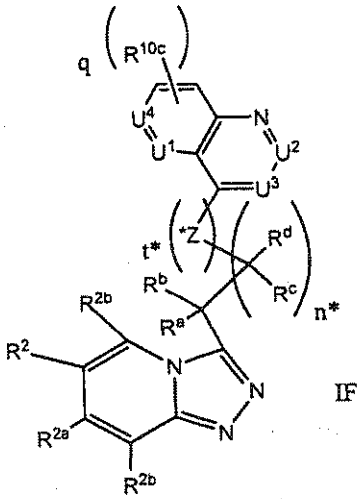
IIA

enantiomers, diastereomers, salts and solvates thereof, wherein variables R^a, R^b, R^c, R^d, R^1, R^2, R^{2a}, R^{2b}, R^3, Z, Z*, n, q and t are as previously defined above. Preferred compounds of formulae IA, IB, IC, ID and IIA include compounds having any of the preferred R^1 groups and R^2 groups, either alone or in any combination thereof.

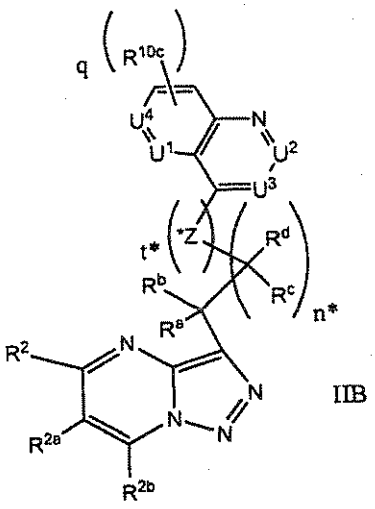
Preferred compounds within the scope of formula I and II also include compounds having the following formula IE, IF, IIB and IIC



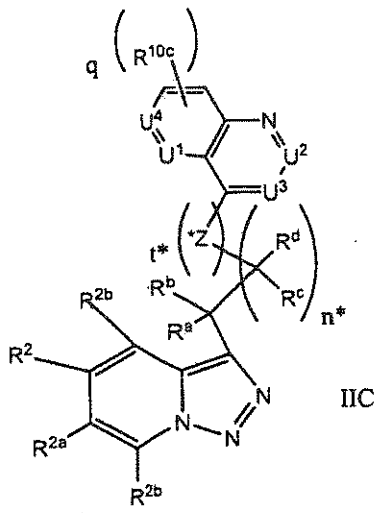
IE



IF



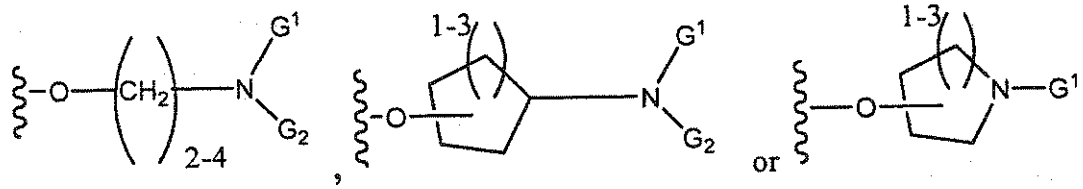
IIB



IIC

enantiomers, diastereomers, salts and solvates thereof

wherein variables R^a, R^b, R^c, R^d, R^2, R^{2a}, R^{2b}, and Z*, are as previously defined above, provided that in compounds of formula IE R^2 is not phenyl substituted with a group



where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring; and further wherein

q is 0, 1, 2 or 3;

n* is 0, 1 or 2;

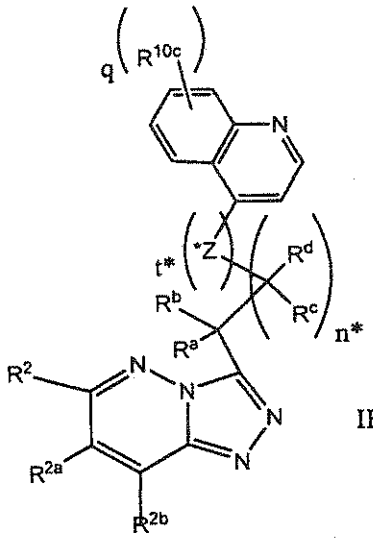
t* is 0 or 1

U^1, U^2, U^3 and U^4 are each independently C, or N; and

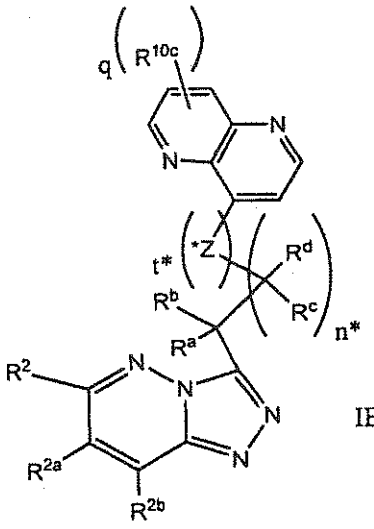
R^{10c} at each occurence is independently selected from the groups listed in the definition of R^{10} previously described above.

Preferred compounds of formulae IE, IF, IIB and IIC include compounds having any of the preferred R^2 groups described above.

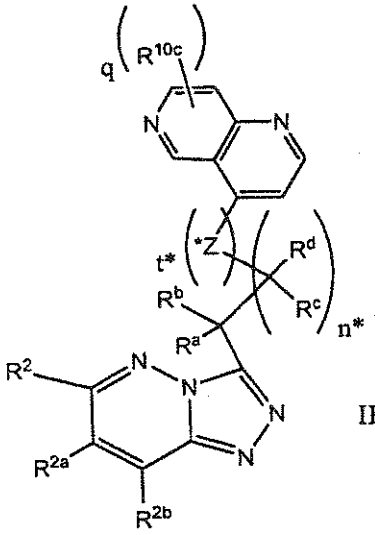
Preferred compounds within the scope of formulae IE and IF include compounds of the following formula IEi, IEii, IEiii, IEiv, IFi, IFii, IFiii and IFiv



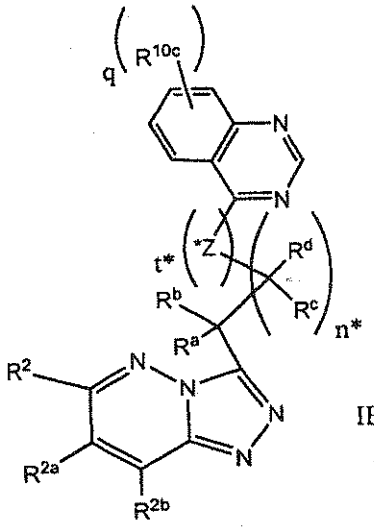
IEi ,



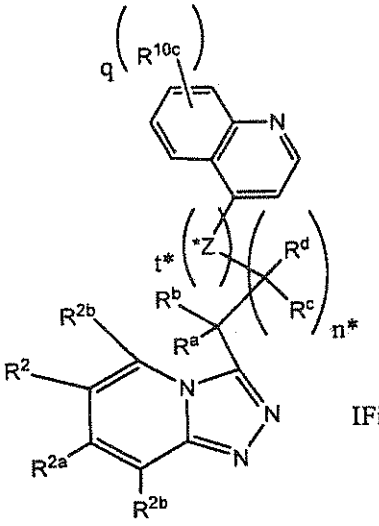
IEii ,



IEiii ,

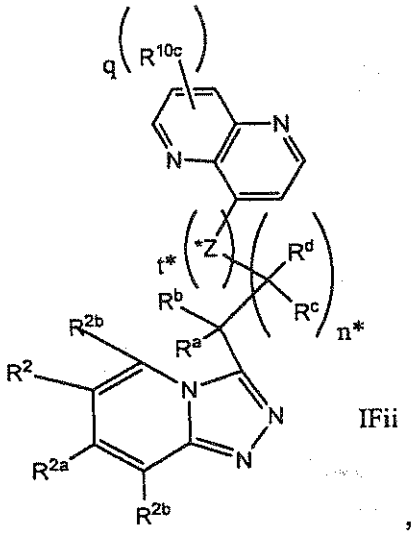


IEiv ,



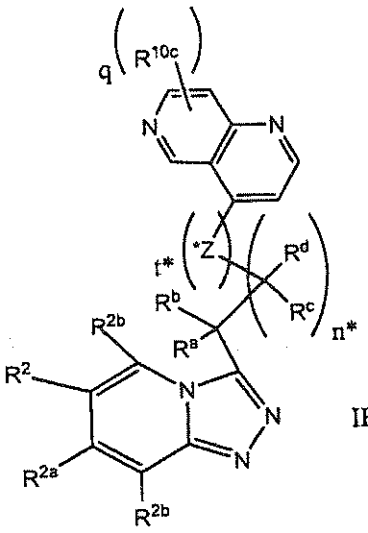
IFi

,



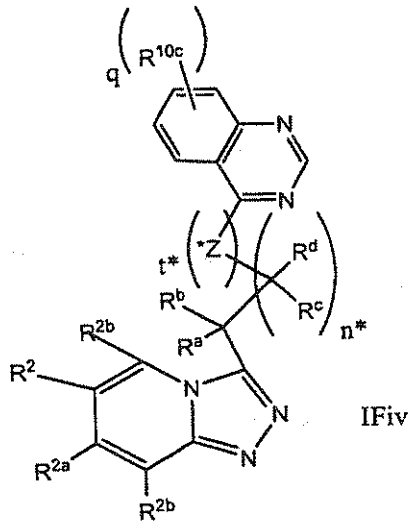
IFii

,



IFiii

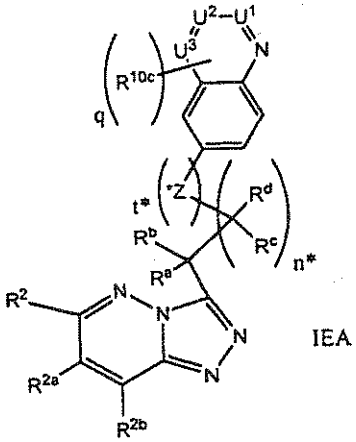
and



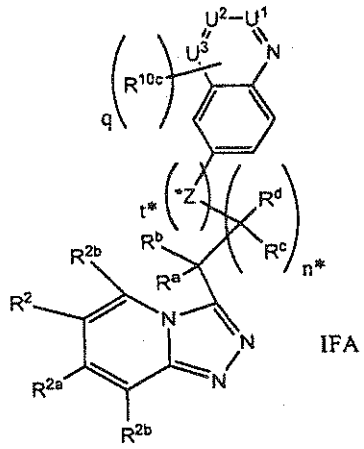
IFiv

enantiomers, diastereomers, salts and solvates thereof.

Preferred compounds within the scope of formula I further include compounds of the following formula IEA and IFA

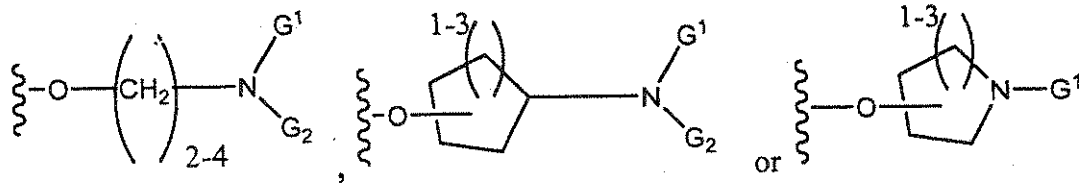


IEA



IFA

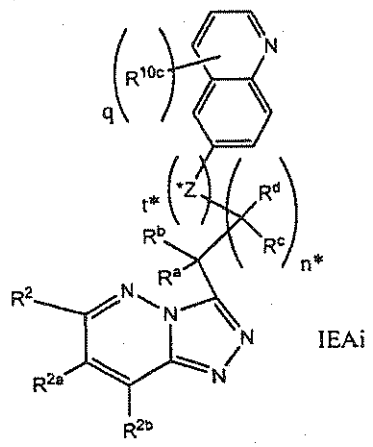
enantiomers, diastereomers, salts and solvates thereof wherein variables R^a, R^b, R^c, R^d, R^2, R^{2a}, R^{2b}, R^{10c}, U^1, U^2, U^3, Z*, n*, q, and t*are as previously defined above provided that in compounds of formula IEA R^2 is not phenyl substituted with a group



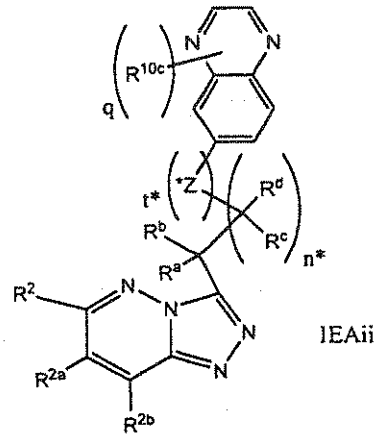
where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring. .

Preferred compounds of formulae IEA and IFA include compounds having any of the preferred R^2 groups described above.

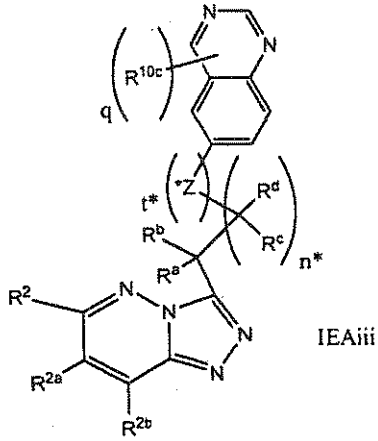
Preferred compounds of formulae IEA and IFA include compounds of formulae IEAi, IEAii, IEAiii, IFAi, IFAii and IFAiii



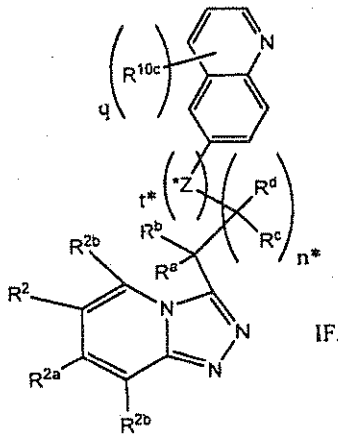
IEAi



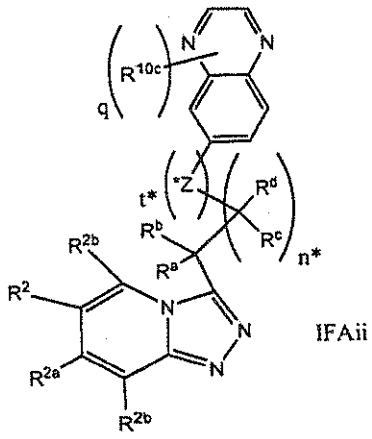
IEAii



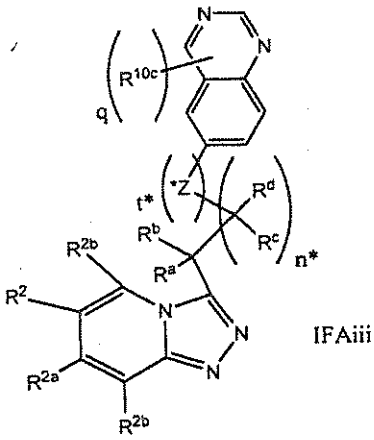
IEAiii



IFAi



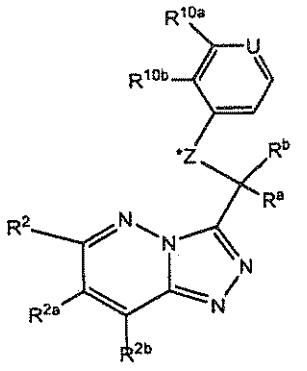
IFAii

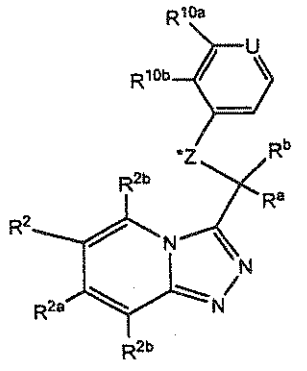


IFAiii

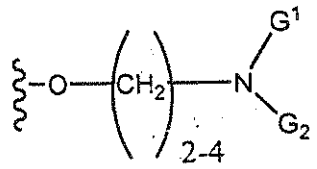
enantiomers, diastereomers, salts and solvates thereof.

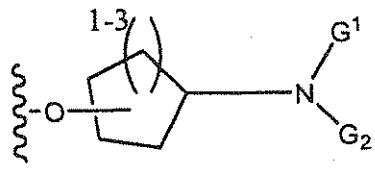
Preferred compounds within the scope of formula I further include compounds of the following formula IG or IH

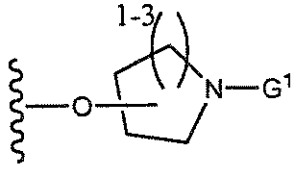

IG


IH

Wherein U is CR^{10c} or N, and variables R^a, R^b, R^2, R^{2a}, R^{2b}, R^{10a}, R^{10b}, R^{10c}, and Z*, are as previously defined above, provided that in compounds of formula IG R^2 is not phenyl substituted with a group

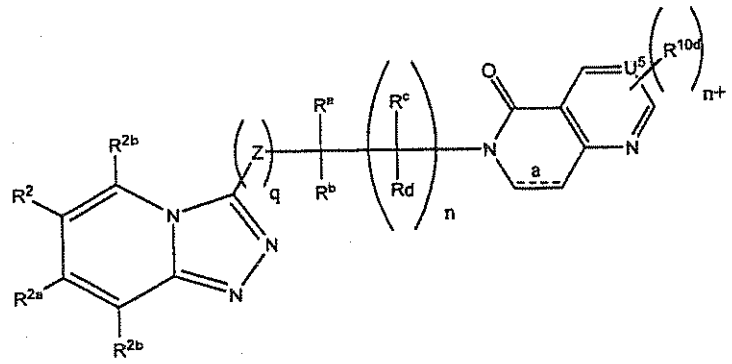

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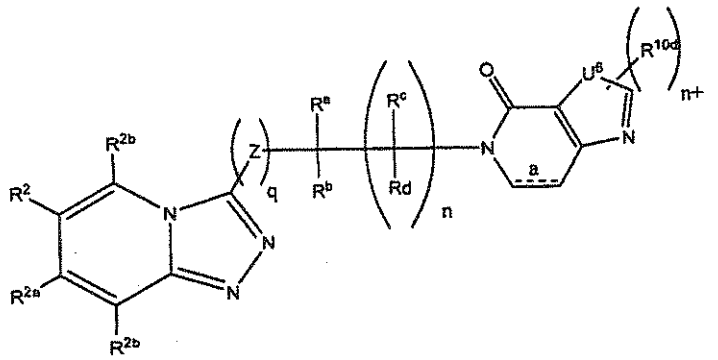

or



where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring. Preferred compounds of formulae IG and IH include compounds having any of the preferred R^2 groups described above.

Preferred compounds within the scope of formula I further include compounds of the following formula IJ or IK


IJ


IK

Where a is a bond or is absent; U^5 is C or N; U^6 is NH, O or S; and m+ is 0, 1, 2 or 3. Preferred compounds of formulae IJ and IK include compounds having any of the preferred R^2 groups described above.

Preferred compounds of the present invention include the compounds exemplified herein.

The invention also relates to pharmaceutical compositions containing the above compounds, together with a pharmaceutically acceptable vehicle or carrier.

The invention also relates to a method of treating cancer in a subject using the above compounds.

The invention also relates to a method of reducing tumor size in a subject using the above compounds.

The invention also relates to a method of reducing metastasis in a tumor in a subject, using the above compounds.

The invention also relates to a method of treating HGF-mediated disorders in a subject using the above compounds.

INDICATIONS

Compounds of the present invention would be useful for, but not limited to, the prevention or treatment of angiogenesis related diseases. The compounds of the invention have c-Met inhibitory activity. The compounds of the invention are useful in therapy as antineoplasia agents or to minimize deleterious effects of HGF.

Compounds of the invention would be useful for the treatment of neoplasia including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma,

teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

Preferably, the compounds are useful for the treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

The compounds also would be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

The compounds of the invention are useful in therapy of proliferative diseases. These compounds can be used for the treatment of an inflammatory rheumatoid or rheumatic disease, especially of manifestations at the locomotor apparatus, such as various inflammatory rheumatoid diseases, especially chronic polyarthritis including rheumatoid arthritis, juvenile arthritis or psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis, such as systemic Lupus erythematosus, poly-myositis, dermato-myositis, systemic sclerodermia or mixed collagenosis; postinfectious arthritis (where no living pathogenic organism can be found at or in the affected part of the body), seronegative spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; or further any combinations thereof. An example of an inflammation related disorder is (a) synovial inflammation, for example, synovitis, including any of the particular forms of synovitis, in particular bursal synovitis and purulent synovitis, as far as it is not crystal-induced. Such synovial inflammation may for example, be consequential to or associated with disease, e.g. arthritis, e.g. osteoarthritis, rheumatoid arthritis or arthritis deformans. The present invention is further applicable to the systemic treatment of inflammation, e.g. inflammatory diseases or conditions, of the joints or locomotor apparatus in the region of the tendon insertions and tendon sheaths. Such inflammation may be, for example, consequential to or associated with disease or further (in a broader sense of the invention) with surgical intervention, including, in particular conditions such as insertion endopathy, myofasciale syndrome and tendomyosis. The present invention is further especially applicable to the treatment of inflammation, e.g. inflammatory disease or condition, of connective tissues including dermatomyositis and myositis.

These compounds can be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome)) since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

Further, some of these compounds can be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease. The compounds will also be useful in treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome).

The compounds of the present invention are also useful in the treatment of ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis.

The compounds of the present invention are also useful in the treatment of conditions wherein undesired angiogenesis, edema, or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, Kaposi's sarcoma, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, and inflammatory rheumatoid or rheumatic disease. The compounds are also useful in the reduction of subcutaneous fat and for the treatment of obesity.

The compounds of the present invention are also useful in the treatment of ocular conditions such as ocular and macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, glaucoma, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration.

The compounds of the present invention are also useful in the treatment of cardiovascular conditions such as atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease.

The compounds of the present invention are also useful in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukemia and lymphoma, tumor-induced pleural or pericardial effusions, and malignant ascites.

The compounds of the present invention are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy.

The compounds of the present invention are also useful in the reduction of blood flow in a tumor in a subject.

The compounds of the present invention are also useful in the reduction of metastasis of a tumor in a subject.

The compounds of this invention may also act as inhibitors of other protein kinases, e.g. tie-2, lck, src, fgf, c-Met, ron, ckit and ret, and thus be effective in the treatment of diseases associated with other protein kinases.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

As used herein, the compounds of the present invention include the pharmaceutically acceptable derivatives thereof.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt and the like.

DEFINITIONS

"Angiogenesis" is defined as any alteration of an existing vascular bed or the formation of new vasculature, which benefits tissue perfasion. This includes the formation of new vessels by sprouting of endothelial cells from existing blood vessels or the remodeling of existing vessels to alter size, maturity, direction or flow properties to improve blood perfusion of tissue.

As used herein, "HGF" refers to hepatocyte growth factor/scatter factor. This includes purified hepatocyte growth factor/scatter factor, fragments of hepatocyte growth factor/scatter factor, chemically synthesized fragments of hepatocyte growth factor/scatter factor, derivatives or mutated versions of hepatocyte growth factor/scatter factor, and fusion proteins comprising

hepatocyte growth factor/scatter factor and another protein. "HGF" as used herein also includes hepatocyte growth factor/scatter factor isolated from species other than humans.

As used herein "c-Met" refers to the receptor for HGF. This includes purified receptor, fragments of receptor, chemically synthesized fragments of receptor, derivatives or mutated versions of receptor, and fusion proteins comprising the receptor and another protein. "c-Met" as used herein also includes the HGF receptor isolated from a species other than humans.

As used herein, "HGF" refers to hepatocyte growth factor/scatter factor. This includes purified hepatocyte growth factor/scatter factor, fragments of hepatocyte growth factor/scatter factor, chemically synthesized fragments of hepatocyte growth factor/scatter factor, derivatives or mutated versions of hepatocyte growth factor/scatter factor, and fusion proteins comprising hepatocyte growth factor/scatter factor and another protein. "HGF" as used herein also includes hepatocyte growth factor/scatter factor isolated from species other than humans.

As used herein "c-Met" refers to the receptor for HGF. This includes purified receptor, fragments of receptor, chemically synthesized fragments of receptor, derivatives or mutated versions of receptor, and fusion proteins comprising the receptor and another protein. "c-Met" as used herein also includes the HGF receptor isolated from a species other than humans.

As used herein, the terms "hepatocyte growth factor" and "HGF" refer to a growth factor typically having a structure with six domains (finger, Kringle 1, Kringle 2, Kringle 3, Kringle 4 and serine protease domains). Fragments of HGF constitute HGF with fewer domains and variants of HGF may have some of the domains of HGF repeated; both are included if they still retain their respective ability to bind a HGF receptor. The terms "hepatocyte growth factor" and "HGF" include hepatocyte growth factor from humans ("huHGF") and any non-human mammalian species, and in particular rat HGF. The terms as used herein include mature, pre, pre-pro, and pro forms, purified from a natural source, chemically synthesized or recombinantly produced. Human HGF is encoded by the cDNA sequence published by Miyazawa et al. (1989), supra, or Nakamura et al. (1989), supra. The sequences reported by Miyazawa et al. and Nakamura et al. differ in 14 amino acids. The reason for the differences is not entirely clear; polymorphism or cloning artifacts are among the possibilities. Both sequences are specifically encompassed by the foregoing terms. It will be understood that natural allelic variations exist and can occur among individuals, as demonstrated by one or more amino acid differences in the amino acid sequence of each individual. The terms "hepatocyte growth factor" and "HGF" specifically include the delta 5 huHGF as disclosed by Seki et al., supra.

The terms "HGF receptor" and "c-Met" when used herein refer to a cellular receptor for HGF, which typically includes an extracellular domain, a transmembrane domain and an intracellular domain, as well as variants and fragments thereof which retain the ability to bind HGF. The terms "HGF receptor" and "c-Met" include the polypeptide molecule that comprises the full-length, native amino acid sequence encoded by the gene variously known as p190.sup.MET. The present definition specifically encompasses soluble forms of HGF receptor, and HGF receptor from natural sources, synthetically produced in vitro or obtained by genetic manipulation including methods of recombinant DNA technology. The HGF receptor variants or fragments preferably share at least about 65% sequence homology, and more preferably at least about 75% sequence homology with any domain of the human c-Met amino acid sequence published in Rodrigues et al., Mol. Cell. Biol., 11:2962-2970 (1991); Park et al., Proc. Natl. Acad. Sci., 84:6379-6383 (1987); or Ponzetto et al., Oncogene, 6:553-559 (1991).

The terms "agonist" and "agonistic" when used herein refer to or describe a molecule which is capable of, directly or indirectly, substantially inducing, promoting or enhancing HGF biological activity or HGF receptor activation.

The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer, pancreatic cancer, cervical cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. While the term "cancer" as used herein is not limited to any one specific form of the disease, it is believed that the methods of the invention will be particularly effective for cancers which are found to be accompanied by increased levels of HGF or expression of c-Met in the mammal.

The terms "treating," "treatment," and "therapy" as used herein refer to curative therapy, prophylactic therapy, and preventative therapy.

The term "mammal" as used herein refers to any mammal classified as a mammal, including humans, cows, horses, dogs and cats. In a preferred embodiment of the invention, the mammal is a human.

Given that elevated levels of c-Met and HGF are observed in hypertension, arteriosclerosis, myocardial infarction, and rheumatoid arthritis, nucleic acid ligands will serve as useful therapeutic agents for these diseases.

The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals).

A "pharmaceutically-acceptable derivative " denotes any salt, ester of a compound of this invention, or any other compound which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl. The term "lower alkyl substituted with R^2" does not include an acetal moiety.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are

lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

Alkyl, alkylenyl, alkenyl, and alkynyl radicals may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1 or more substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy, lower alkylamino, and the like. Phenyl substituted with -O-CH_2-O- forms the aryl benzodioxolyl substituent.

The term "heterocyclyl" (or "heterocyclo") embraces saturated, and partially saturated and heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-,-O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino, lower alkylamino, and the like.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl, dihydrothiazolyl, and the like.

Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

The term heterocyclyl, (or heterocyclo) also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g.,

benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl].

The term "heteroaryl" denotes aryl ring systems that contain one or more heteroatoms selected from the group O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quarternized. Examples include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfamyl radicals are independently substituted with one or two alkyl radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-.

The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals independently substituted with one or two alkyl radicals, respectively.

More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The terms "heterocyclylalkylenyl" and "heterocyclylalkyl" embrace heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH_3S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups, which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups, which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C_1-C_3-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups, which have been independently substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three

carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminomethoxyethoxy, N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH_2 groups.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C_1-C_3-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C_3-C_6 rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "5-6-

membered cycloalkylalkyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups include C_3-C_6 rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

The term(s) "Formulas I, II, III, IV, V, VI and VII" either alone or in combination includes any sub formulas.

The compounds of the invention are endowed with c-Met inhibitory activity.

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of c-Met.

The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the current invention in association with a least one pharmaceutically acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically effective amount of a compound of the current invention.

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a

substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of the current invention may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567,

Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI

International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of α-carotene, α-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTC, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanlne derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole

derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone,

miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Alternatively, the present compounds may also be used in co-therapies with VEGFR inhibitors including:

AMG 706 (motesanib diphosphate);

N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-1-phthalazinamine;

4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide;

N-[2-(diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide;

3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide;

N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine;

3-[5,6,7,13-tetrahydro-9-[(1-methylethoxy)methyl]-5-oxo-12H-indeno[2,1-a]pyrrolo[3,4-c]carbazol-12-yl]propyl ester N,N-dimethyl-glycine;

N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;

N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine

N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((3-(1,3-oxazol-5-yl)phenyl)amino)-3-pyridinecarboxamide;

2-(((4-fluorophenyl)methyl)amino)-N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide.

6-fluoro-N-(4-(1-methylethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

2-((4-pyridinylmethyl)amino)-N-(3-(((2S)-2-pyrrolidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-(3-(1,1-dimethylethyl)-1H-pyrazol-5-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3,3-dimethyl-2,3-dihydro-1-benzofuran-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-((((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

2-((4-pyridinylmethyl)amino)-N-(3-((2-(1-pyrrolidinyl)ethyl)oxy)-4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(4-(pentafluoroethyl)-3-(((2S)-2-pyrrolidinylmethyl)oxy)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-((3-azetidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-(4-piperidinyloxy)-5-(trifluoromethyl)phenyl)-2-((2-(3-pyridinyl)ethyl)amino)-3-pyridinecarboxamide;

N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;

2-(1H-indazol-6-ylamino)-N-[3-(1-methylpyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-[1-(2-dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(1H-indazol-6-ylamino)-nicotinamide;

2-(1H-indazol-6-ylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;

N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;

N-[4-(tert-butyl)-3-(3-piperidylpropyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide;

N-[5-(tert-butyl)isoxazol-3-yl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide; and

N-[4-(tert-butyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide.

Other compounds described in the following patents and patent applications can be used in combination therapy: US 6,258,812, US 2003/0105091, WO 01/37820, US 6,235,764, WO 01/32651, US 6,630,500, US 6,515,004, US 6,713,485, US 5,521,184, US 5,770,599, US 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, US 5,990,141, WO 00/12089 and WO 00/02871.

In some embodiments, the combination comprises a composition of the present invention in combination with at least one anti-angiogenic agent. Agents are inclusive of, but not limited to, *in vitro* synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or

stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

Exemplary anti-tumor agents include HERCEPTIN™ (trastuzumab), which may be used to treat breast cancer and other forms of cancer, and RITUXAN™ (rituximab), ZEVALIN™ (ibritumomab tiuxetan), and LYMPHOCIDE™ (epratuzumab), which may be used to treat non-Hodgkin's lymphoma and other forms of cancer, GLEEVAC™ which may be used to treat chronic myeloid leukemia and gastrointestinal stromal tumors, and BEXXAR™ (iodine 131 tositumomab) which may be used for treatment of non-Hodgkins's lymphoma.

Exemplary anti-angiogenic agents include ERBITUX™ (IMC-C225), KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as ABX-EGF (panitumumab), IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). The pharmaceutical compositions of the present invention can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-met".

Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., US Publication No. 2003/0162712; US Patent No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, US Patent No. 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., US Publication No. 2002/0042368), specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (US Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide.(Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055,(Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands) DAC:antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical, USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA); CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson, USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis inhibitor, (Trigen, UK); TBC-1635, (Encysive Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567, (Abbott, USA); Metastatin, (EntreMed, USA); angiogenesis inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-methoxyestradiol, (Oncology Sciences Corporation, USA); ER-68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93, (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142, (Fujisawa, Japan, JP 02233610); platelet factor 4, (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist, (Borean, Denmark); cancer therapy, (University of South Carolina, USA); bevacizumab (pINN), (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alpha5beta3 integrin, second generation, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); enzastaurin hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor, (Alchemia, Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen, Australia); cilengitide (pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2-methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research

Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenesis, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); anginex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 beta1, (Protein Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia); heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan); VEGF receptor modulators, (Pharmacopeia, USA); VE-cadherin-2 antagonists , (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA);vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan);

TumStatin, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as VEGF antagonists, other kinase inhibitors including p38 inhibitors, KDR inhibitors, EGF inhibitors and CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, NSAID's, or $\alpha_v\beta_3$ inhibitors.

The present invention comprises processes for the preparation of a compound of Formula I, II, III, IV, V, VI and VII.

Also included in the family of compounds of the current are the pharmaceutically acceptable salts and solvates thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the current invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the current invention include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, aistidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the

invention by reacting, for example, the appropriate acid or base with the compound of the current invention. When a basic group and an acid group are present in the same molecule, a compound of the current invention may also form internal salts.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the general procedures described in WO 08/008539 (the entirety of which is incorporated herein by reference) as well as those illustrated in the example compounds described below.

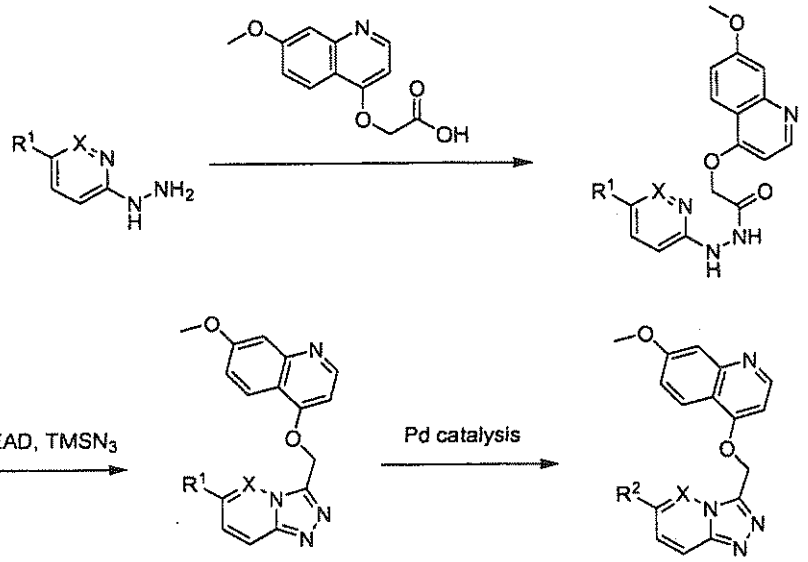
The following abbreviations are used throughout the specification:

HOAc	-	acetic acid
MeCN, CH_3CN	-	acetonitrile
NH_3	-	ammonia
NH_4Cl	-	ammonium chloride
Ar	-	argon
HBTA	-	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HATU	-	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
PyBop	-	benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate
$Pd_2(dba)_3$	-	bis(dibenzylideneacetone) palladium
BINAP	-	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
TEAC	-	bis(tetra-ethylammonium)carbonate
BBr_3	-	boron tribromide
BSA	-	bovine serum albumin
Br_2	-	bromine
BOC	-	butyloxycarbonyl
Cs_2CO_3	-	cesium carbonate
$CHCl_3$	-	chloroform
$CDCl_3$	-	chloroform deuterated
Cu	-	copper
CuI	-	copper(I) iodide
Et_2O	-	diethyl ether
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	-	diisobutylaluminum hydride

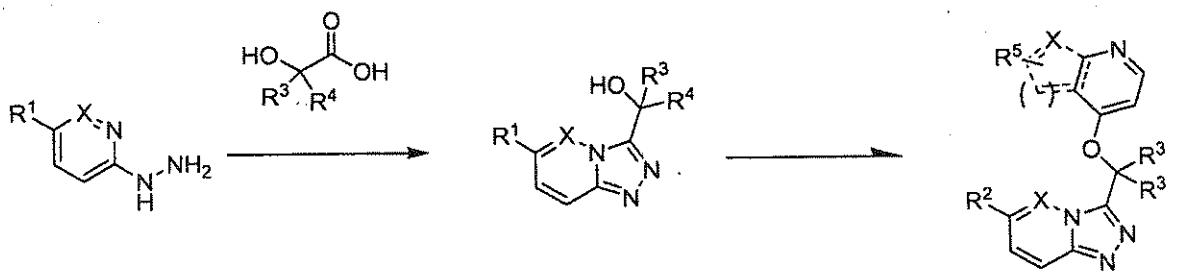
DIAD	-	diisopropyl azodicarboxylate
DIEA	-	diisopropylethylamine
DMF	-	dimethylformamide
DMAP	-	4-dimethylaminopyridine
DMSO	-	dimethylsulfoxide
EDC, EDCI	-	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
dppa	-	diphenylphosphoryl azide
EtOAc	-	ethyl acetate
FBS	-	fetal bovine serum
g	-	gram
h	-	hour
HBr	-	hydrobromic acid
HCl	-	hydrochloric acid
HOBt	-	1-hydroxybenzotriazole hydrate
H_2	-	hydrogen
H_2O_2	-	hydrogen peroxide
Fe	-	iron
LiHMDS	-	lithium bis(trimethylsilyl)-amide
LDA	-	Lithium diisopropylamide
MCPBA	-	*meta*-chloroperbenzoic acid
$MgSO_4$	-	magnesium sulfate
MeOH, CH_3OH	-	methanol
MeI	-	methyl iodide
CH_2Cl_2, DCM	-	methylene chloride
NMP	-	N-methylpyrrolidinone
ML, ml	-	milliliter
N_2	-	nitrogen
Pd/C	-	palladium on carbon
$Pd(OAc)_2$	-	palladium acetate
$Pd(OH)_2$	-	palladium hydroxide
$Pd(PPh_3)_4$	-	palladium tetrakis triphenylphosphine
$Pd(dppf)Cl_2$	-	1,1-bis(diphenylphosphino)ferrocene palladium chloride
PBS	-	phosphate buffered saline
$POCl_3$	-	phosphorous oxychloride

	K_2CO_3	-	potassium carbonate
	KOH	-	potassium hydroxide
	RT	-	room temperature
	$NaHCO_3$	-	sodium bicarbonate
	$NaBH_4$	-	sodium borohydride
	$NaBH_3CN$	-	sodium cyanoborohydride
	NaOtBu	-	sodium tert-butoxide
	NaOH	-	sodium hydroxide
	$NaClO_2$	-	sodium chlorite
	NaCl	-	sodium chloride
	$NaHPO_4$	-	sodium biphospate
	NaH	-	sodium hydride
	NaI	-	sodium iodide
	Na_2SO_4	-	sodium sulfate
	TBTU	-	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
	THF	-	tetrahydrofuran
	Et_3N, TEA	-	triethylamine
	TFA	-	trifluoroacetic acid
	P(*t*-bu)$_3$	-	tri(tert-butyl)phosphine
	H_2O	-	water

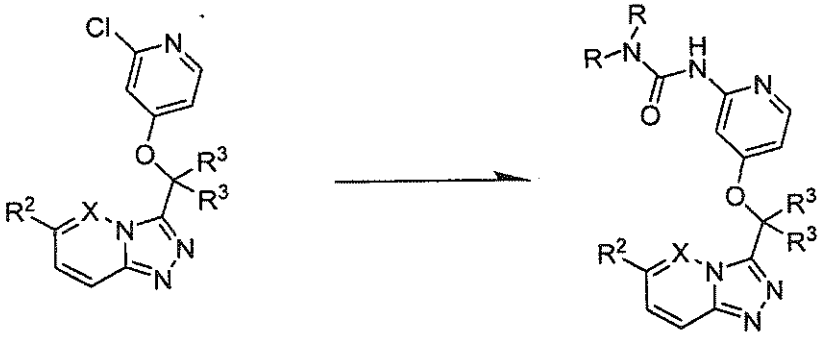
General Method A



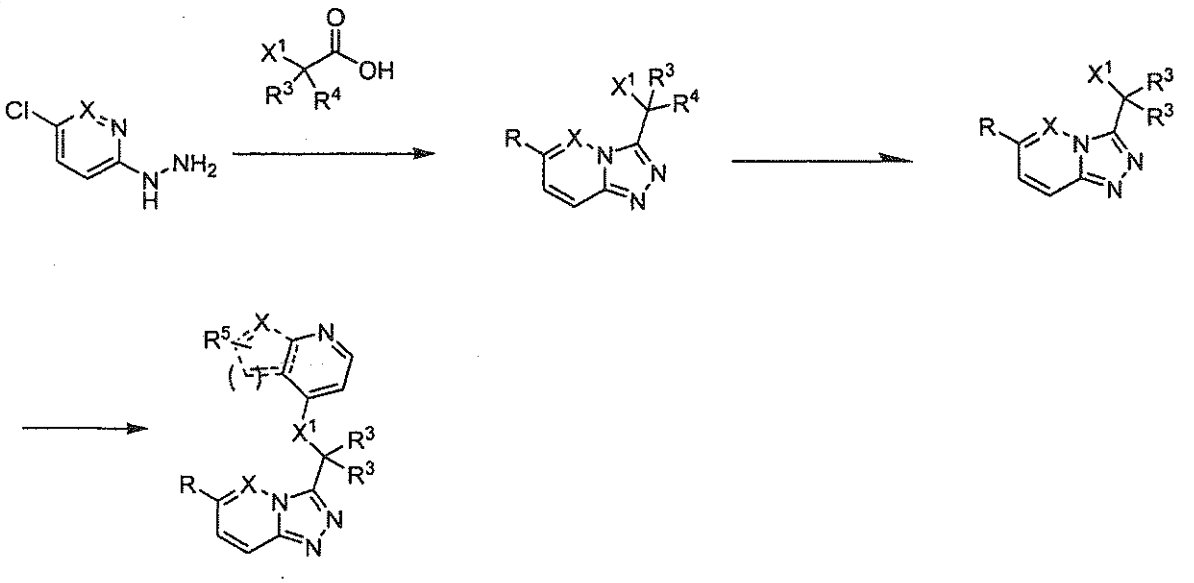
General Method B



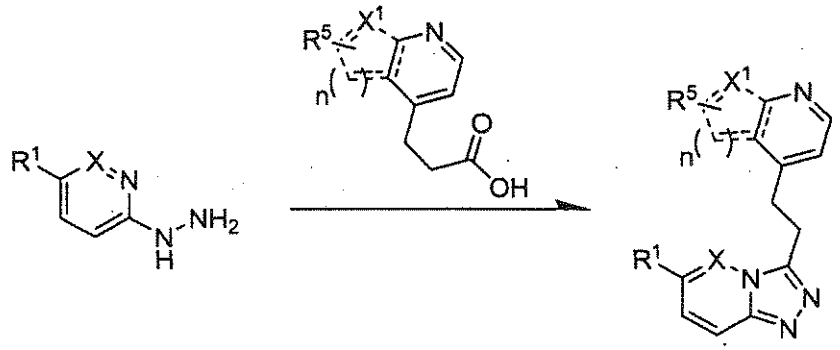
General Method C



General Method D

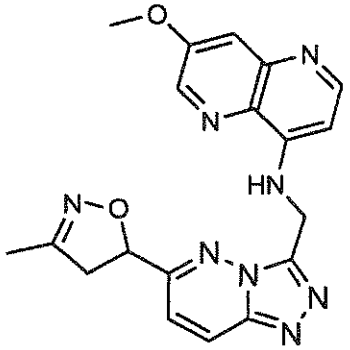


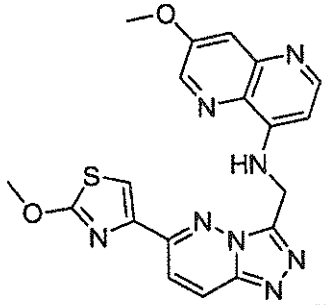
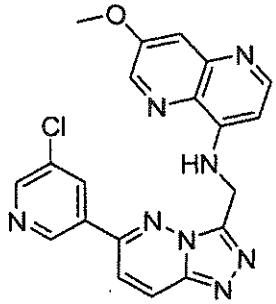
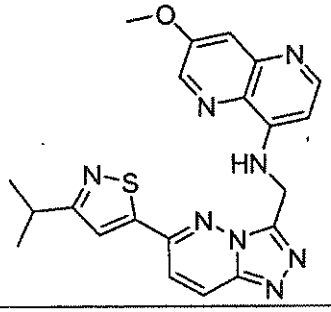
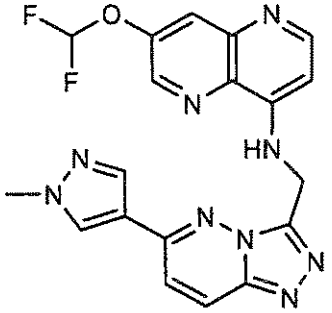
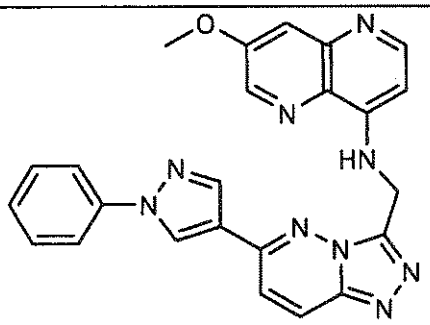
General Method E

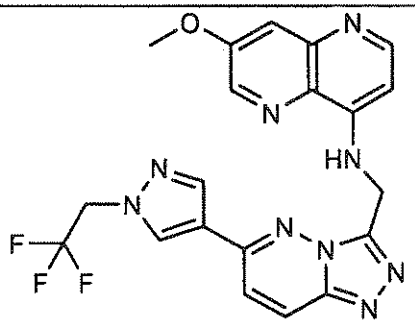
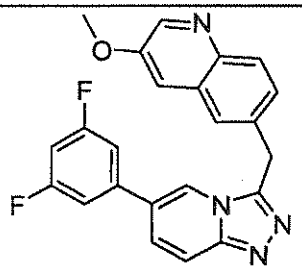
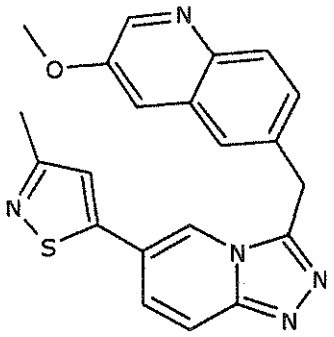
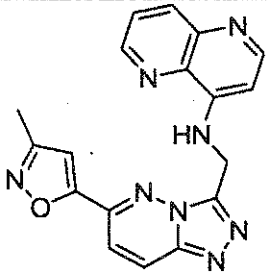
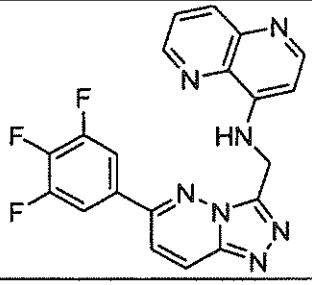


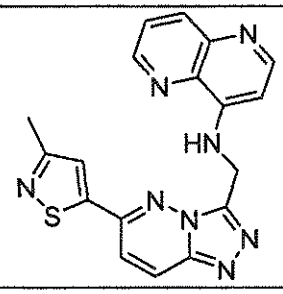
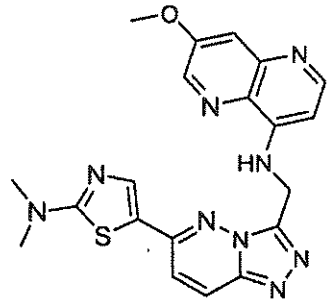
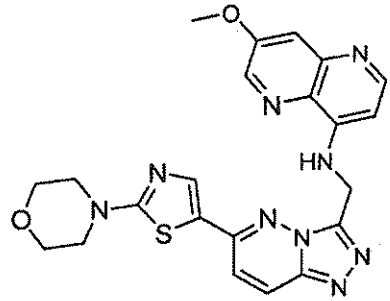
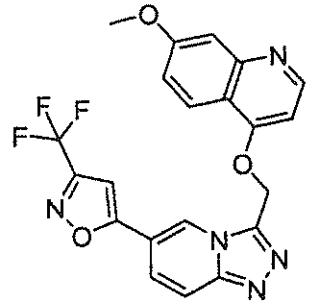
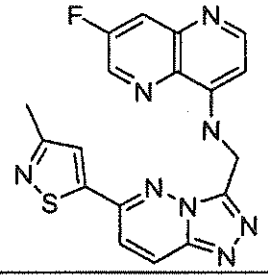
Examples 1-343

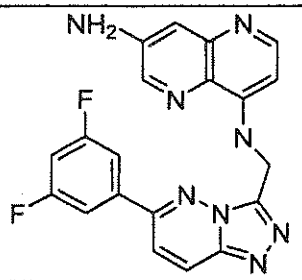
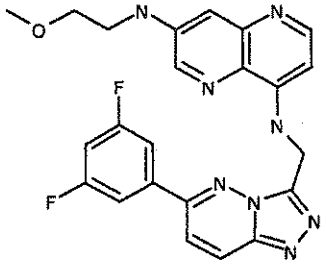
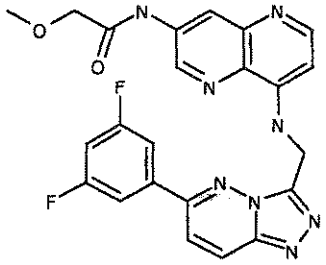
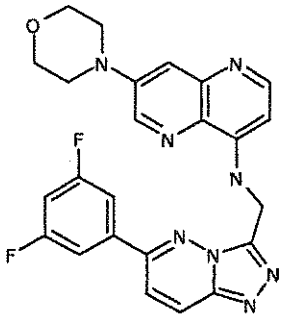
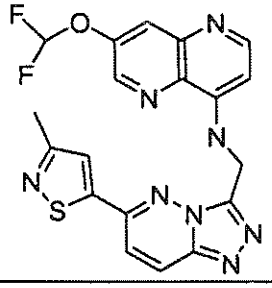
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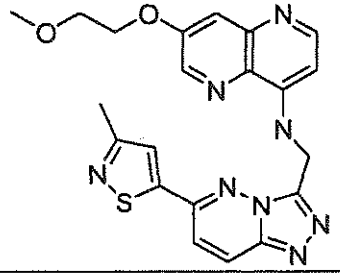
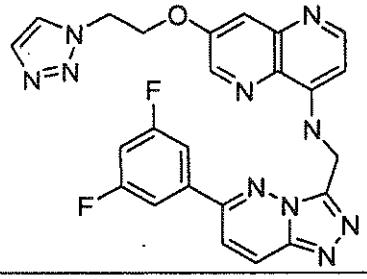
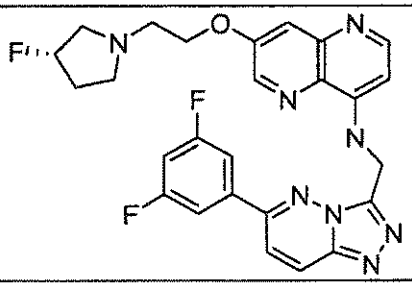
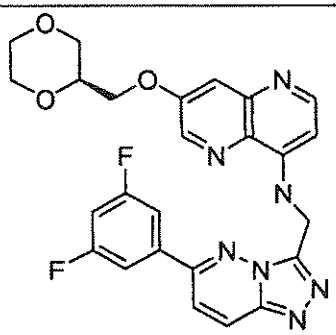
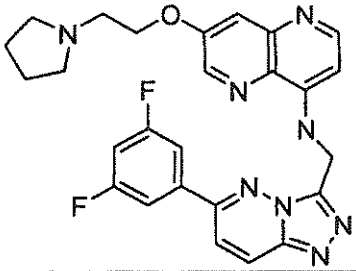
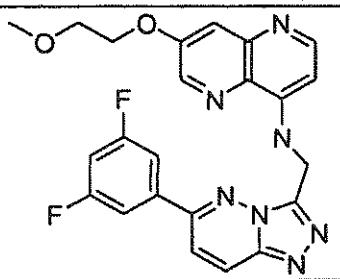
EX.	Structure	MW	Mass Found	General Method
344		390	391	D

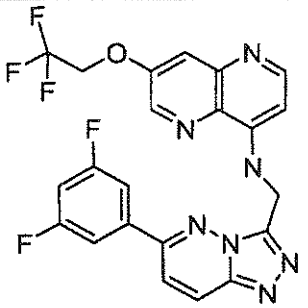
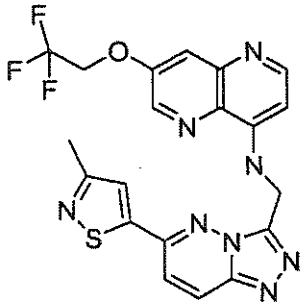
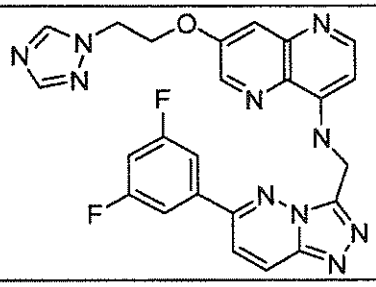
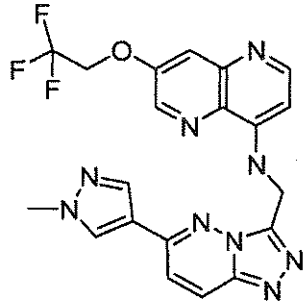
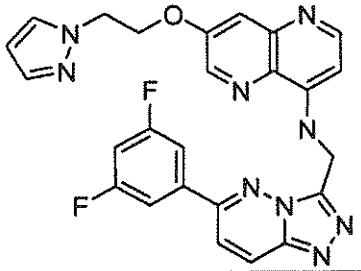
EX.	Structure	MW	Mass Found	General Method
345		420	421	D
346		418	419	D
347		432	433	D
348		423	424	D
349		449	450	D

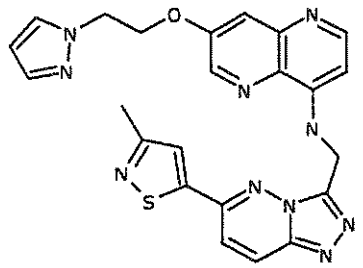
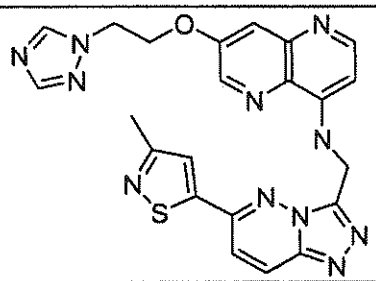
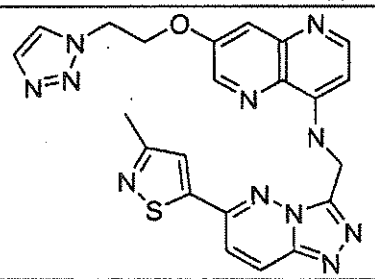
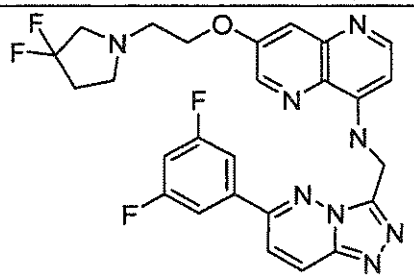
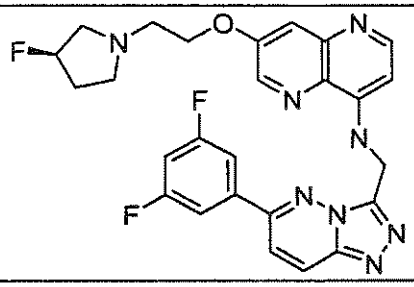
EX.	Structure	MW	Mass Found	General Method
350		455	456	D
351		402	403	A
352		387	388	A
353		358	359	D
354		407	408	D

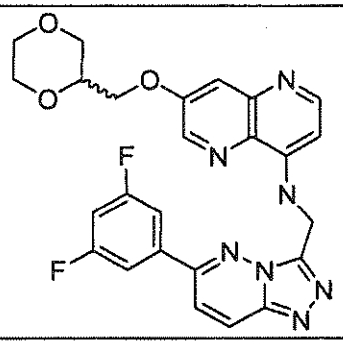
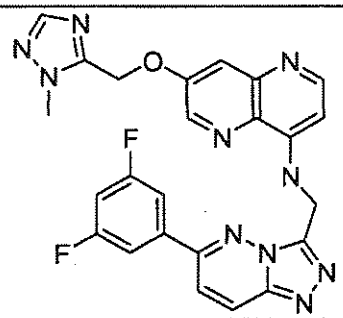
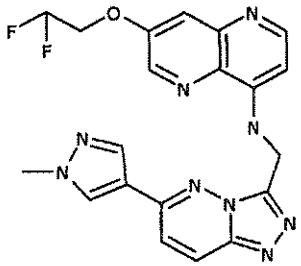
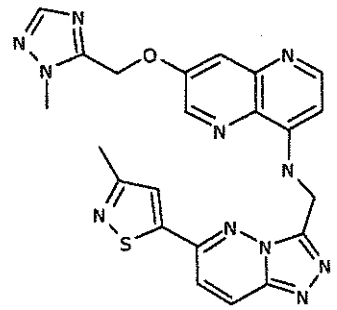
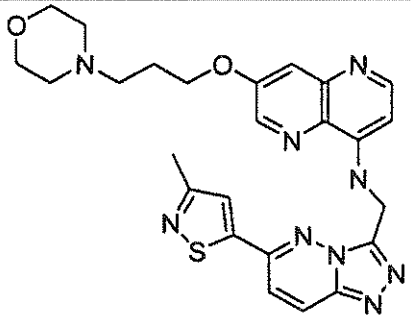
EX.	Structure	MW	Mass Found	General Method
355		374	375	D
356		433	434	D
357		475	476	D
358		441	442	A
359		392	393	D

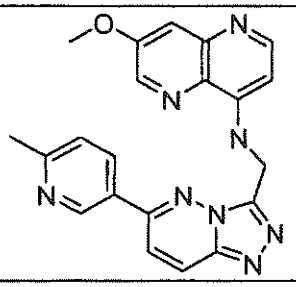
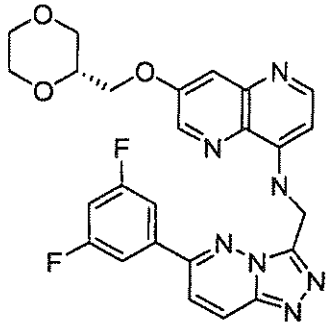
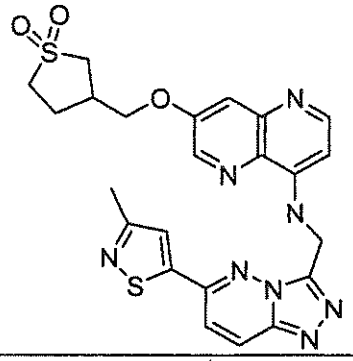
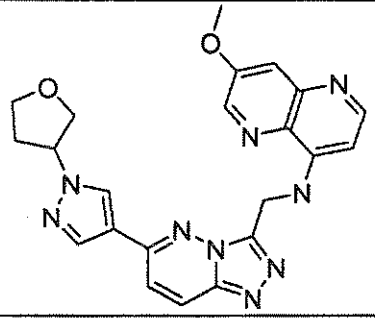
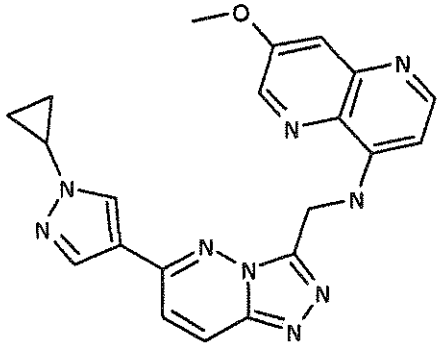
EX.	Structure	MW	Mass Found	General Method
360		404	405	D
361		462	463	D
362		476	477	D
363		474	475	D
364		440	441	D

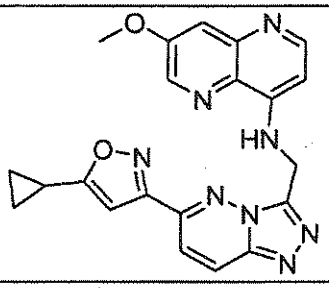
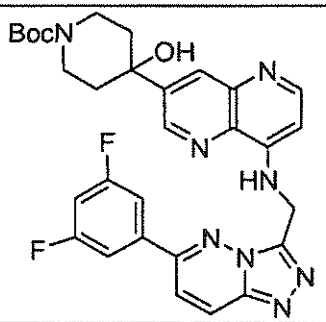
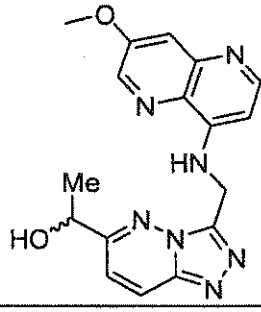
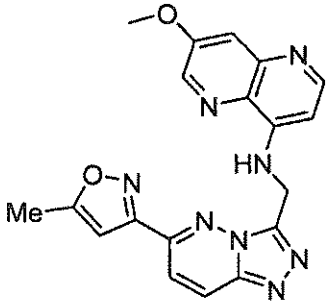
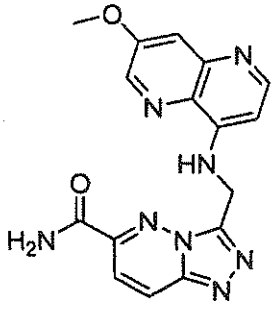
EX.	Structure	MW	Mass Found	General Method
365		448	449	D
366		500	501	D
367		520	521	D
368		505	506	D
369		502	503	D
370		463	464	D

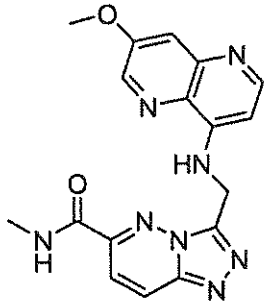
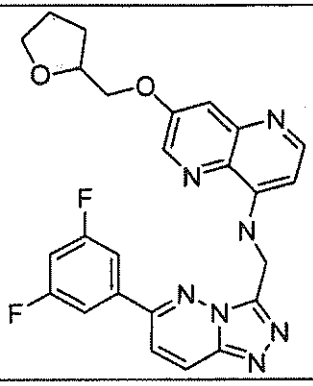
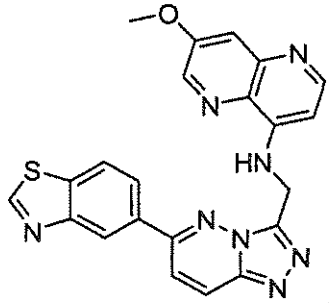
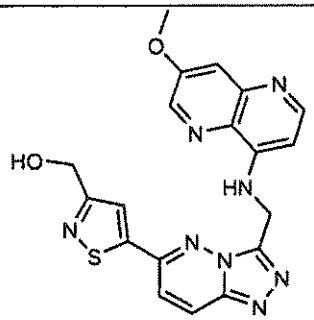
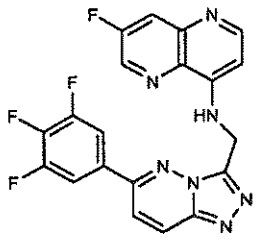
EX.	Structure	MW	Mass Found	General Method
371		487	488	D
372		472	473	D
373		500	501	D
374		455	456	D
375		499	500	D

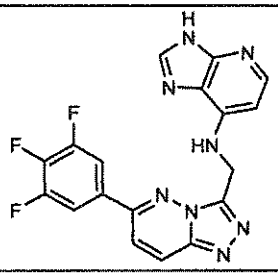
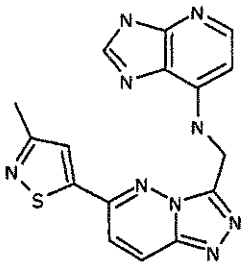
EX.	Structure	MW	Mass Found	General Method
376		484	485	D
377		485	486	D
378		485	485	D
379		538	539	D
380		520	521	D

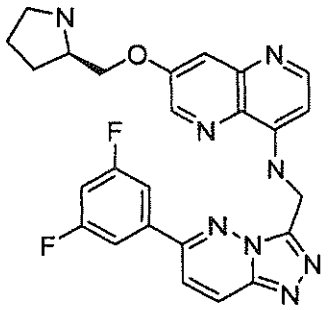
EX.	Structure	MW	Mass Found	General Method
381		505	506	D
382		500	501	D
383		437	438	D
384		485	486	D
385		517	518	D

EX.	Structure	MW	Mass Found	General Method
386		398	399	D
387		505	506	D
388		522	523	D
389		443	444	D
390		413	414	D

EX.	Structure	MW	Mass Found	General Method
391		414	415	D
392		488	489	D
393		351	352	D
394		388	388	D
395		350	351	D

EX.	Structure	MW	Mass Found	General Method
396		364	365	D
397		489	490	D
398		440	441	D
399		420	421	D
400		425	426	D

EX.	Structure	MW	Mass Found	General Method
401		396	397	D
402		363	364	D

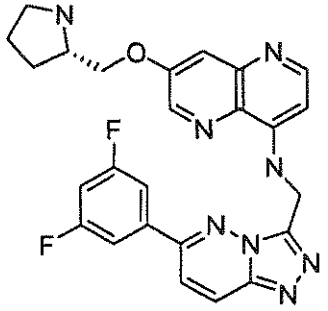


Example 403

(R)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine

a) (R)-tert-butyl 2-((8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yloxy)methyl)pyrrolidine-1-carboxylate was prepared according to method D.

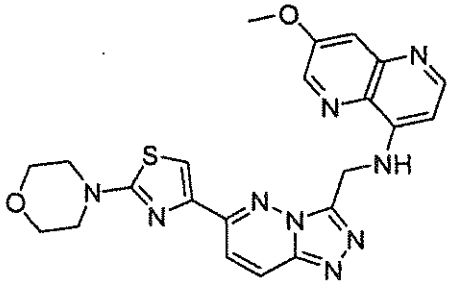
b) (R)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine. The title compound was prepared from (R)-tert-butyl 2-((8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yloxy)methyl)pyrrolidine-1-carboxylate following the procedure used to make 7-methoxy-4-((6-(6-(piperazin-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methoxy)quinoline. *m/z*: 489 (M+H). Calc'd. for $C_{25}H_{22}F_2N_8O$ – 488.



Example 404

(S)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine

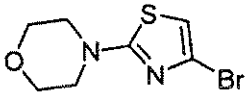
The title compound was prepared in the same manner as (R)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine. *m/z*: 489 (M+H). Calc'd. for $C_{25}H_{22}F_2N_8O$ – 488.



Example 405

7-methoxy-*N*-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine

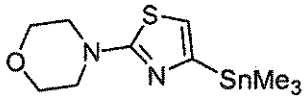
1) 4-(4-bromothiazol-2-yl)morpholine



To a microwave vial was added *N,N*-diisopropylethylamine (0.86 ml, 4.9 mmol), 2,4-dibromothiazole (1.00 g, 4.1 mmol), and morpholine (0.43 ml, 4.9 mmol) in EtOH (4 mL). The mixture was heated under microwave irradiation at 140 °C for 35 minutes. The reaction mixture was concentrated in vacuo. The crude material was dissolved in minimal

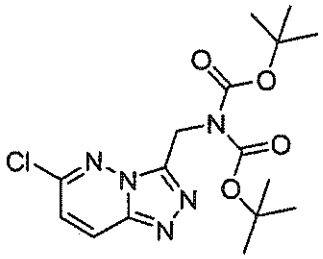
DCM/MeOH and purified via MPLC (eluting with 0-30% EtOAc in hexnaes) to yield 4-(4-bromothiazol-2-yl)morpholine (0.700 g, 68% yield) as a white solid.

2) 4-(4-(trimethylstannyl)thiazol-2-yl)morpholine



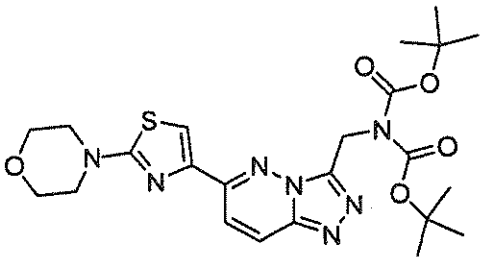
Prepared in a method similar to 3-methyl-5-trimethylstannyl)isothiazole.

3) Bis-tert-butyl(6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methylcarbamate



Di-tert-butyl dicarbonate (24.42 g, 111.9 mmol) was added to a stirred suspension of tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (10.58 g, 37.3 mmol) in acetonitrile (200 mL) at 0°C followed by 4-dimethylaminopyridine (4.556 g, 37.3 mmol). Stirring was continued at 0°C for ~10 min then the cooling bath was removed and stirring was continued at room temperature overnight. The reaction mixture was concentrated in vacuo, diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification via MPLC (EtOAc/MeOH: 100/0 to 90/10) afforded the title compound (14.3g, 37.3 mmol, 100% yield).

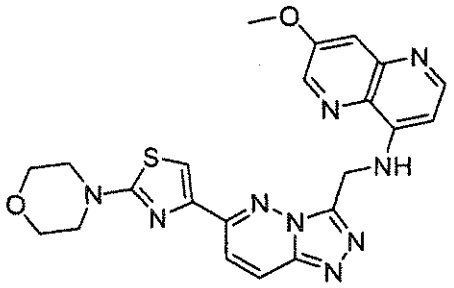
4) (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate



To a pressure vessel purged with argon was added palladium (II) acetate (0.0029 g, 0.013 mmol), Xantphos (0.015 g, 0.026 mmol) and bis-tert-butyl(6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methylcarbamate (0.100 g, 0.26 mmol) in 1,4-dioxane (0.17 M, 1.5 mL). 4-

(4-(trimethylstannyl)thiazol-2-yl)morpholine (0.13 g, 0.39 mmol) and degassed water (0.0094 ml, 0.52 mmol) were added, once more purging the flask with argon. The reaction mixture was stirred at 100 °C for 4h until complete consumption of the starting material. The reaction mixture was concentrated in vacuo. The crude material was dissolved in minimal EtOAc and purified via MPLC (eluting with 100% EtOAc). (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate (0.086 g, 64% yield) was obtained as a solid. The material was carried forward without further purification.

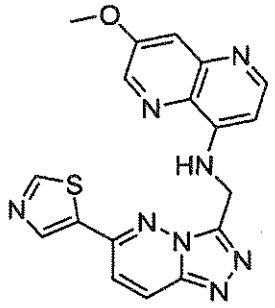
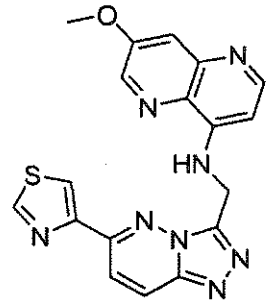
5) 7-methoxy-*N*-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine



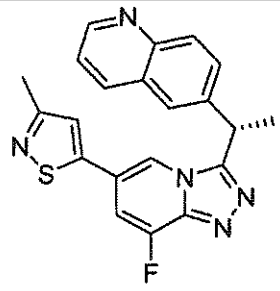
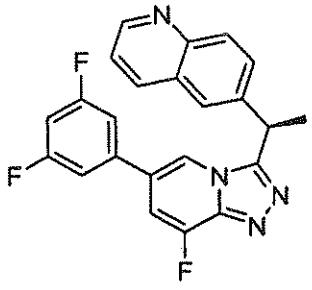
To a microwave vial was added (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate (0.086 g, 0.17 mmol) and 8-chloro-3-methoxy-1,5-naphthyridine (0.036 g, 0.18 mmol) in 2-butanol (1.0 mL). The vial was sealed and heated under microwave irradiation at 120 °C for 6 h. The reaction was concentrated in vacuo. The crude material was dissolved in 2M ammonia in methanol and purified via MPLC (eluting with 0-10% 1% NH_4OH/ in DCM). 7-methoxy-N-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine (0.031 g, 39% yield) was obtained as a yellow solid. *m/z*: 476.0 (M+H). Calc'd. for $C_{22}H_{21}N_9O_2S$ – 475.53.

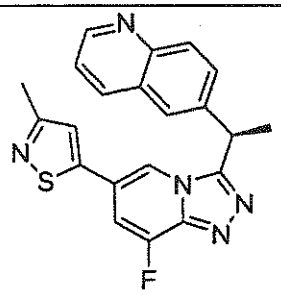
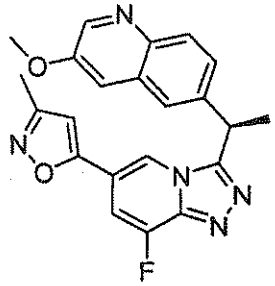
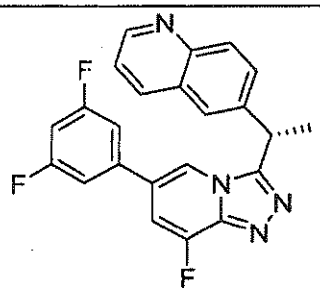
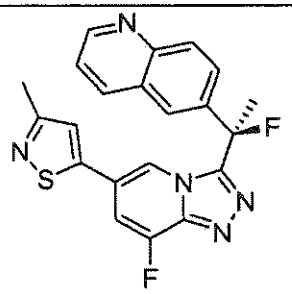
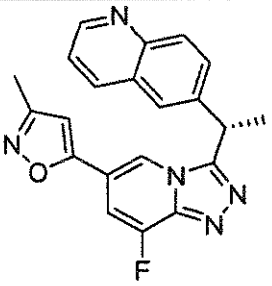
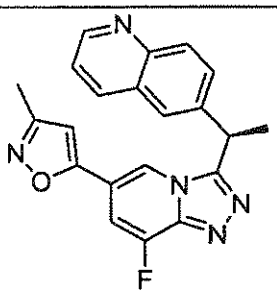
The following example compounds 406 and 407 were prepared using the method to make 7-methoxy-*N*-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine:

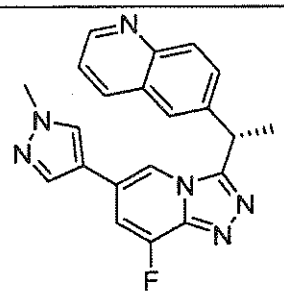
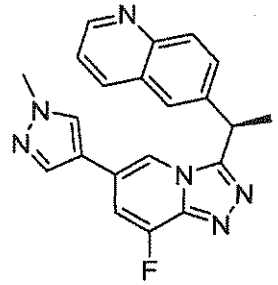
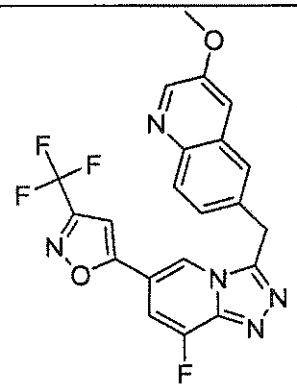
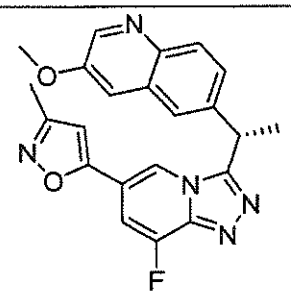
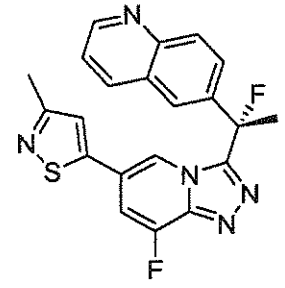
Ex	Structure	MW	Mass Found

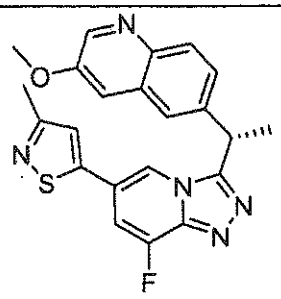
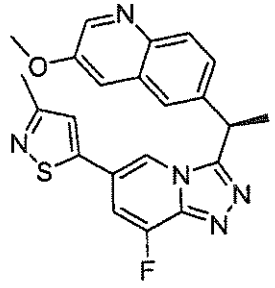
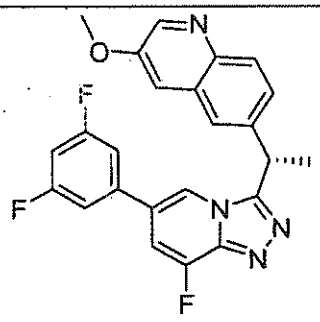
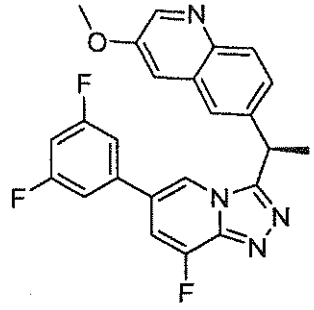
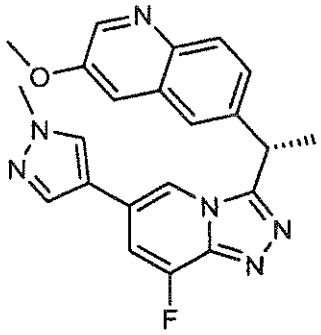
406		390	391
407		390	391

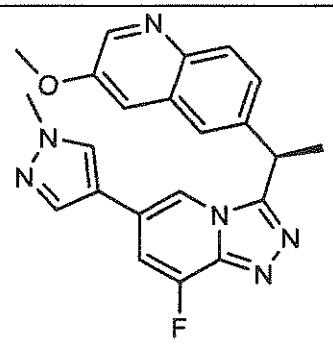
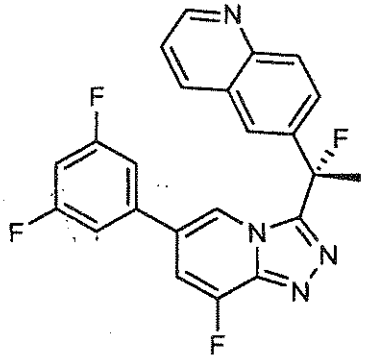
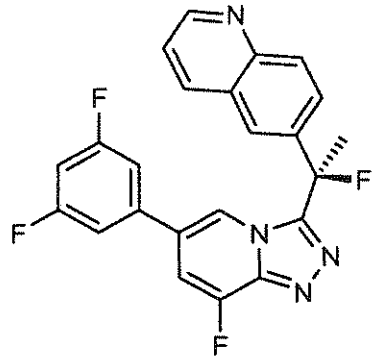
The following example compounds 408-428 were prepared using steps 1 and 2 of Method A. Where applicable, enantiomer was obtained via SFC:

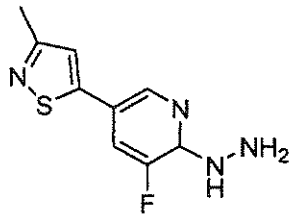
Ex	Structure	MW	Mass Found
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409		404	405

410		389	389
411		403	404
412		404	405
413		407	408
414		373	374
415		373	374

416		372	373
417		372	373
418		443	444
419		403	404
420		407	408

421		419	420
422		419	420
423		434	435
424		434	435
425		402	403

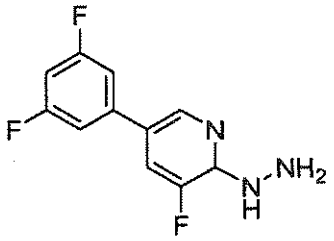
426		402	403
427		422	423
428		422	423



1-(3-fluoro-5-(3-methylisothiazol-5-yl)pyridin-2-yl)hydrazine

5-chloro-2,3-difluoropyridine (0.069 ml, 0.67 mmol), X-Phos (0.045 g, 0.094 mmol) and palladium (II) acetate (0.011 g, 0.047 mmol) were combined in 1,4-dioxane (0.2 M, 3.4 mL). To the reaction vessel was added 3-methyl-5-(trimethylstannyl)isothiazole (0.53 g, 2.0 mmol) and, after purging with argon, the reaction was stirred at 100 °C for 2h and then concentrated in vacuo. The crude material was dissolved in minimal DCM and purified via MPLC (eluting first with 100% EtOAc followed by 20% EtOAc in hexanes -isocratic) to yield 2,3-difluoro-5-(3-methylisothiazol-5-yl)pyridine (0.139 g, 98% yield) as a yellow solid. 2,3-difluoro-5-(3-

methylisothiazol-5-yl)pyridine was converted to the title compound using a procedure similar to 1-(4-methyl-6-phenylpyridazin-3-yl)hydrazine.



1-(5-(3,5-difluorophenyl)-3-fluoropyridin-2-yl)hydrazine

A mixture of palladium (II) acetate (0.0375 g, 0.167 mmol), potassium phosphate (2.13 g, 10.0 mmol), 3,5-difluorophenylboronic acid (1.58 g, 10.0 mmol), X-Phos (0.159 g, 0.334 mmol) and 5-chloro-2,3-difluoropyridine (0.347 ml, 3.34 mmol) was diluted with 1,4-dioxane (0.1M, 33.4 mL) and water (0.3M, 11.0 mL) and was heated under nitrogen at 100 °C for 45 minutes. The reaction was concentrated in vacuo. The concentrated material was triturated with water, filtered and rinsed with MeCN. The crude solid was taken up in dichloromethane and filtered over a plug of Celite to eliminate residual palladium. The material was dissolved in minimal DCM, and purified via MPLC (eluting with 0-10% EtOAc in hexanes) to yield 5-(3,5-difluorophenyl)-2,3-difluoropyridine. The material was converted to the hydrazine in a method similar to that in the synthesis of (*S*)-6-(1-(8-fluoro-6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)ethyl)quinoline.

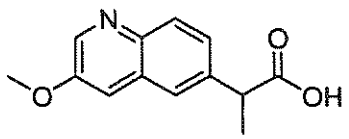
The following compounds were prepared using a similar method as 1-(5-(3,5-difluorophenyl)-3-fluoropyridin-2-yl)hydrazine:

1) 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazin

The following compounds were prepared using a similar method (using either the trimethyl- or tributyl- stannnane) as 1-(3-fluoro-5-(3-methylisothiazol-5-yl)pyridin-2-yl)hydrazine:

1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine; and
1-(3-fluoro-5-(3-trifluoromethylisoxazol-5-yl)pyridin-2-yl)hydrazine.

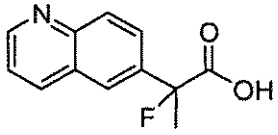
HCl



2-(3-methoxyquinolin-6-yl)propanoic acid hydrochloride

Tert-butyl 2-(3-methoxyquinolin-6-yl)propanoate (0.865 g, 3.01 mmol) was dissolved in EtOAc (0.2M, 15 mL), and HCl (g) (0.0915 ml, 3.01 mmol) was bubbled through the solution for approximately 5 minutes. The reaction vessel was sealed and the reaction was stirred at room temperature for 1.5h until completion. The reaction mixture was concentrated in vacuo to yield 2-(3-methoxyquinolin-6-yl)propanoic acid hydrochloride (0.805 g, 99.9% yield) as an orange solid.

2.5NaCl

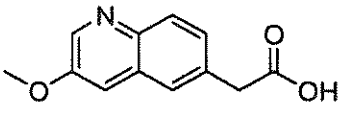


2-fluoro-2-(quinolin-6-yl)propanoic acid

To a solution of methyl 2-(quinolin-6-yl)propanoate (0.868 g, 4.03 mmol) in THF (1.1M, 3.7 mL) at -78 °C was added LiHMDS (1M in THF) (5.24 ml, 5.24 mmol). The reaction was stirred at -78 °C for ~15 minutes, then to it was added a solution of N-fluorobenzenesulfonimide (1.40 g, 4.44 mmol) in THF(1.0M, 4.5 mL). The reaction was allowed to warm to -10 °C over 2h. The reaction was filtered through a plug of Celite, washed with EtOAc and the filtrate was then concentrated in vacuo. The concentrated material was rediluted with EtOAc and washed with saturated NH_4Cl solution. The aqueous layer was then extracted with EtOAc, and the organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was dissolved in minimal DCM and purified via MPLC (eluting with isocratic 40% EtOAc:Hexanes to yield methyl 2-fluoro-2-(quinolin-6-yl)propanoate (0.709 g, 75.4% yield) as a yellow oil.

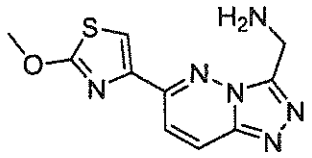
To synthesize the corresponding acid, methyl 2-fluoro-2-(quinolin-6-yl)propanoate was saponified in a method similar to that of 2-(quinolin-6-yl)propanoic acid.

HCl



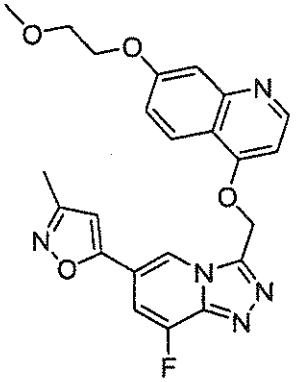
2-(3-methoxyquinolin-6-yl)acetic acid hydrochloride

tert-Butyl 2-(3-methoxyquinolin-6-yl)acetate was saponified in a method similar to 2-(3-methoxyquinolin-6-yl)propanoic acid hydrochloride.



(6-(2-methoxythiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methanamine

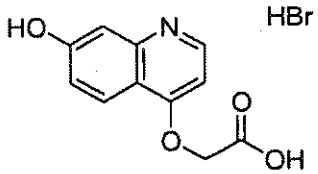
The di-tert-butyl carbonate precursor ((6-(2-methoxy-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate) was synthesized in a method similar to (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate, using 2-methoxy-4-(tributylstannyl)thiazole as the organostannane, followed by TFA deprotection similar to the method described for (6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methanamine.



Example 429

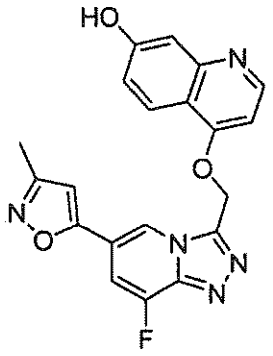
4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)methoxy)-7-(2-methoxyethoxy)quinoline

1) 2-(7-hydroxyquinolin-4-yloxy)acetic acid hydrobromide



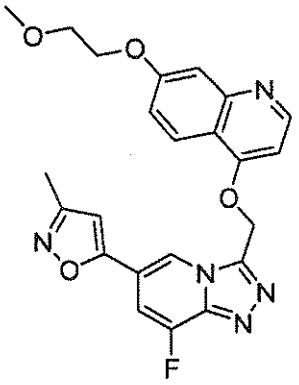
To a pressure vial was added 2-(7-methoxyquinolin-4-yloxy)acetic acid (1.00 g, 4.29 mmol) in DCE (0.6 M, 7 mL). The vial was cooled in an ice bath and to the solution was added BBr_3 (1.62 ml, 17.2 mmol). The reaction was allowed to warm to room temperature and stirred overnight. While some starting material remained, the reaction was stopped and diluted with DCM (keep in hood due to fuming). The solids were filtered and dried over high vacuum to yield a light brown crude solid (~1.8g). The material was used without further purification.

2) 4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol

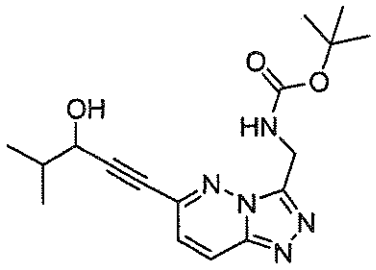


The material was prepared using general method A (with 2-(7-hydroxyquinolin-4-yloxy)acetic acid hydrobromide and 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine

3) 4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-7-(2-methoxyethoxy)quinoline

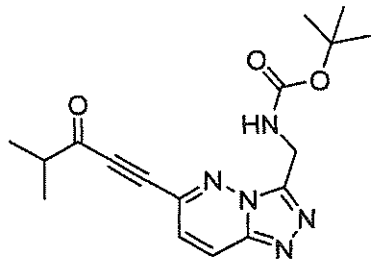


4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol (0.110 g, 0.28 mmol), PPh_3 (polymer supported: 2.3 mmol/g) (1.2 g, 2.8 mmol) and 2-methoxyethanol (0.11 ml, 1.3 mmol) were combined in DCM (11 ml, 0.28 mmol). The mixture was cooled to 0 °C, and DEAD (0.089 ml, 0.56 mmol) was added dropwise. The reaction was removed from the ice bath, and stirred at RT for 1h. The material was diluted with DCM, and the PS-PPh_3 was filtered off and washed thoroughly with DCM. The filtrate was concentrated in vacuo. The crude material was dissolved in minimal DCM and purified via MPLC (eluting with 0-100% 90:10:1 DCM:MeOH:NH_4OH in DCM) to yield 4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-7-(2-methoxyethoxy)quinoline (0.070 g, 55% yield) as a white solid. MS (ESI pos. ion) m/z: 450.0 (M+H). Calc'd Exact Mass for $C_{23}H_{20}FN_5O_4$: 449.44



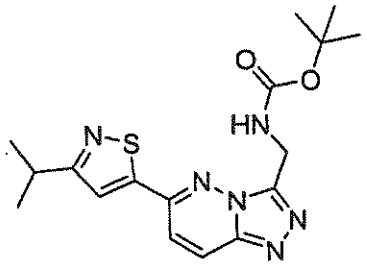
tert-Butyl (6-(3-hydroxy-4-methylpent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

In a 15-mL sealed tube flushed with nitrogen, tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (2.00 g, 7.0 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.58 g, 0.70 mmol), and copper (I) iodide (0.34 g, 1.8 mmol) were diluted in MeCN (70 mL). To the reaction mixture was first added 4-methylpent-1-yn-3-ol (3.7 ml, 35 mmol), followed by triethylamine (25 ml, 176 mmol). The reaction was then heated at 50 °C for 7.5 h. The crude material was dissolved in minimal DCM and purified via MPLC (twice)(eluting with 0-10% MeOH/NH_4OH:DCM) to yield tert-butyl (6-(3-hydroxy-4-methylpent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (1.823 g, 75% yield) as a light brown solid.



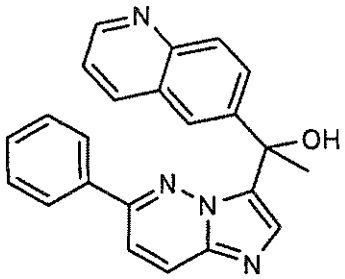
tert-Butyl (6-(4-methyl-3-oxopent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

tert-Butyl (6-(3-hydroxy-4-methylpent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (1.82 g, 5.27 mmol) and manganese dioxide (activated) (9.16 g, 105 mmol) were dissolved in DCM (263 mL) and stirred at room temperature over two days. Additional manganese dioxide (activated) (4.58 g, 52.7 mmol) was added and stirring continued overnight. The reaction mixture was filtered over a plug of Celite and washed with DCM to yield tert-butyl (6-(4-methyl-3-oxopent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.917 g, 50.7% yield) after concentration in vacuo.



tert-Butyl (6-(3-isopropylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

An aqueous mixture of tert-butyl (6-(4-methyl-3-oxopent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.800 g, 2.33 mmol) and hydroxylamine-O-sulfonic acid (0.263 g, 2.33 mol) in water (8.0 mL) and 1,4-dioxane (8.0 mL) was stirred at 0 °C until complete consumption of the organic starting material was observed. The mixture was then carefully treated with solid sodium bicarbonate (0.196 g, 2.33 mmol), followed by treatment with 1.4 M aqueous sodium hydrosulfide (1.83 ml, 2.56 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was diluted with water (20 mL) and extracted with DCM (40 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The concentrated crude material was dissolved in minimal DCM and was purified via MPLC (eluting with 0-10% MeOH/NH_4OH in DCM) to yield tert-butyl (6-(3-isopropylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.196 g, 22.5% yield) with 82% purity. MS (ESI pos. ion) m/z: 433.0 (M+H). Calc'd Exact Mass for $C_{21}H_{20}N_8OS$: 432.51.



Example 430

1-(6-Phenylimidazo[1,2-b]pyridazin-3-yl)-1-(quinolin-6-yl)ethanol

a) N-methoxy-N-methylquinoline-6-carboxamide

A 250 mL RB flask was charged with quinoline-6-carboxylic acid (5.00 g, 28.9 mmol), DCM (100 ml, 1554 mmol), oxalyl chloride (3.79 ml, 43.3 mmol), and a few drops of DMF and stirred at RT for 2 hours, then concentrated. The residue was taken up in DCM (100 ml, 1554 mmol), cooled to 0°C, then Hunig's Base (17.7 ml, 101 mmol) and N-methoxymethanamine hydrochloride (2.96 g, 30.3 mmol) were added slowly. The mixture was stirred at room

temperature for 16 hours (91463-3-1). The mixture was diluted with DCM (200 mL), then washed with water (250 mL), sat. $NaHCO_3$ (250 mL), and brine (250 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated to give a brown oil, which was purified by MPLC eluting with 2-6% MeOH/DCM to give N-methoxy-N-methylquinoline-6-carboxamide (5.943 g, 95.2% yield) as a brown oil.

b) 1-(quinolin-6-yl)ethanone

A 250 mL RB flask was charged with N-methoxy-N-methylquinoline-6-carboxamide (5.943 g, 27.5 mmol) and THF (100 ml, 1220 mmol), then cooled to 0 C. Methylmagnesium bromide (18.3 ml, 55.0 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was not quite complete, so additional MeMgBr (3 mL) was added and the mixture was stirred overnight. The mixture was then neutralized using 2N HCl and the aqueous layer was extracted with DCM (200 mL x 2) and EtOAc (200 mL x 2). The organic layer was dried with $MgSO_4$, filtered, and concentrated to give a yellow oil. The aqueous layer contained some product, so the layer was concentrated and then filtered thru a reverse phase C_{18} column, first eluting with water than with MeOH. The MeOH layer was concentrated to give a yellow oil which was combined with the yellow oil from the organic layer. The combined portions were purified by MPLC eluting with a gradient of 2-6% MeOH/DCM. 1-(quinolin-6-yl)ethanone (4.074 g, 86.6% yield) was isolated as a yellow oil which solidified upon standing.

c) 2-bromo-1-(quinolin-6-yl)ethanone hydrobromide

A 250 mL RB flask was charged with 1-(quinolin-6-yl)ethanone (3.82 g, 22.3 mmol) and 30% HBr/AcOH (45.0 ml). Bromine (1.14 ml, 22.1 mmol) was added slowly. This was stirred at room temperature for 4 hours, at which point full conversion to product (with a small amount of dibrominated side product) was observed. The reaction mixture was filtered and the solid was washed with Et_2O to give 2-bromo-1-(quinolin-6-yl)ethanone hydrobromide (5.6359 g, 76.3% yield). The compound was used in the next step without further purification.

d) (E)-N'-(6-chloropyridazin-3-yl)-N,N-dimethylformamidine

A 500 mL RB flask was charged with 6-chloropyridazin-3-amine (10.0 g, 77.2 mmol) and dimethoxy-N,N-dimethylmethanamine (206 ml, 1544 mmol), equipped with a reflux condenser, then heated to 110°C for 3 hours then left at room temperature for 16 hours. The precipitate was collected by filtration. The mother liqour was concentrated down to give an

yellow solid, which was triturated with EtOAc and collected. The solids were combined to give (E)-N'-(6-chloropyridazin-3-yl)-N,N-dimethylformamidine (11.81 g, 82.9% yield) as a white solid

e) (6-Chloroimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone

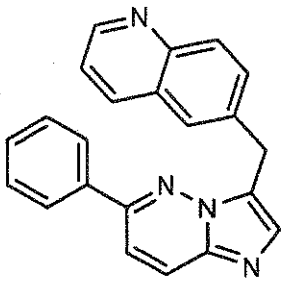
A 100 mL RB flask was charged with 2-bromo-1-(quinolin-6-yl)ethanone (0.7011 g, 2.80 mmol), (E)-N'-(6-chloropyridazin-3-yl)-N,N-dimethylformamidine (0.518 g, 2.80 mmol), and DMF (10.0 ml, 129 mmol), equipped with a reflux condenser, then heated at 105°C for 3 hours. The reaction mixture was concentrated, then triturated with MeOH to yield (6-chloroimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.530 g, 1.72 mmol, 61%) as a brown solid.

f) (6-Phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone

A 48 mL sealed tube was charged with (6-chloroimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.530 g, 1.72 mmol), phenylboronic acid (0.314 g, 2.58 mmol), cesium carbonate (1.68 g, 5.15 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.0701 g, 0.0858 mmol), 1,4-dioxane (6.31 ml, 73.8 mmol), and water (1.11 ml, 61.8 mmol), flushed with argon, sealed, then placed in an 80°C oil bath for 8 hours. The mixture was concentrated then triturated with water, followed by MeOH/DCM to give (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone as a reddish brown solid.

g) 1-(6-Phenylimidazo[1,2-b]pyridazin-3-yl)-1-(quinolin-6-yl)ethanol

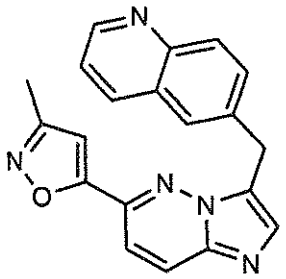
A 25 mL RB flask was charged with (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.200 g, 0.57 mmol) and THF (2.00 ml, 24 mmol), then cooled to 0°C. methylmagnesium bromide (0.76 ml, 2.2 mmol) was added dropwise and the mixture was stirred at room temperature for 5 hours. This was diluted with 2 N HCl (1 mL) and water (25 mL), then extracted with DCM (25 mL x 2) and EtOAc (25 mL). The combined organics were washed with brine and dried with $MgSO_4$, filtered, and concentrated. The resulting oil was purified by MPLC using a 40 g RediSep column, eluting with 2-6% MeOH/DCM over 40 minutes. 1-(6-phenylimidazo[1,2-b]pyridazin-3-yl)-1-(quinolin-6-yl)ethanol (0.082 g, 39% yield) was isolated as a tan solid. MS (ESI pos. ion) m/z: 367 (MH+). Calc'd exact mass for $C_{23}H_{18}N_4O$: 366.



Example 431

6-((6-Phenylimidazo[1,2-b]pyridazin-3-yl)methyl)quinoline

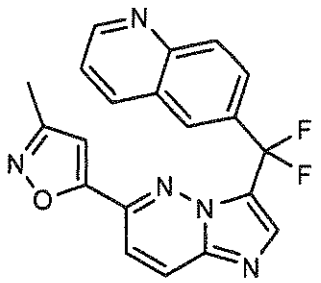
A 10-20 mL microwave vial was charged with hydrazine hydrate (0.0312 ml, 0.642 mmol), (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.150 g, 0.428 mmol), KOH (0.0961 g, 1.71 mmol), and diethylene glycol (4.09 ml, 42.8 mmol), sealed, then placed in a Personal Chemistry microwave at 130°C for 20 minutes after a 5 minute pre-stir. The mixture was diluted with water (75 mL), then extracted with DCM (2 x 75 mL). The combined organics were washed with brine (75 mL), then dried with $MgSO_4$, filtered, and concentrated to give a brown solid, then purified by prep HPLC to give the product as the formic acid salt. MS (ESI pos. ion) m/z: 337 (MH+). Calc'd exact mass for $C_{22}H_{16}N_4$: 336.



Example 432

6-((6-(3-Methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline

A 16 mm test tube was charged with hydrazine hydrate (0.0273 ml, 0.563 mmol), (6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (prepared using a similar procedure as (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone) (0.100 g, 0.281 mmol), sodium tert-butoxide (0.0406 g, 0.422 mmol), and 1-butanol (0.670 ml, 7.32 mmol), sealed, then heated to 150°C for 2 hours (96979-1-1). The mixture was diluted with water, neutralized with 2 N HCl, then extracted with DCM (3 x 30 mL). The combined organics were dried with $MgSO_4$, filtered, then concentrated. 6-((6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline was purified by prep HPLC and isolated as the TFA salt. MS (ESI pos. ion) m/z: 341 (MH+). Calc'd exact mass for $C_{20}H_{15}N_5O$: 341.

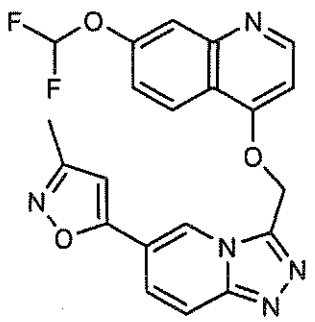


Example 433

6-(difluoro(6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline

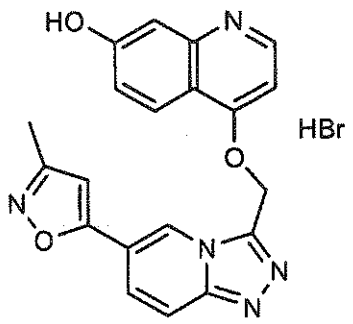
A 25 mm test tube was charged with 2,2-difluoro-1,3-dimethylimidazolidine (DFI) (0.24 g, 1.8 mmol), (6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.125 g, 0.35 mmol), and MeCN (2.00 ml, 38 mmol), sealed, then heated at 84°C for 36 hours, adding additional 2,2-difluoro-1,3-dimethylimidazolidine (DFI) (0.24 g, 1.8 mmol) after 16 hours. The mixture was diluted with water (50 mL), then extracted with DCM (2 x 40 mL). The combined organics were washed with brine (40 mL), dried with $MgSO_4$, filtered, then concentrated to give a brown residue. This was purified by MPLC using a 40 g RediSep column, eluting with 20 - 50% (90:10:1 DCM:MeOH:NH_4OH mixture) in EtOAc over 40 minutes. The purest fractions were collected—these still contained DFI, so the residue was triturated with EtOAc and decanted. 6-(difluoro(6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline was isolated as a light yellow solid.

MS (ESI pos. ion) m/z: 378 (MH+). Calc'd exact mass for $C_{20}H_{13}F_2N_5O$: 377.



Example 434

7-(difluoromethoxy)-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline

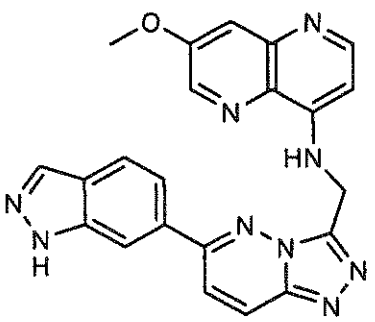


1) 4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol hydrobromide.

A 150 mL tube was charged with 7-methoxy-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline (1.44 g, 3.72 mmol) and HBr (30.3 ml, 558 mmol), sealed, then placed in a 120°C for 5 hours. The reaction mixture was slowly neutralized with 6N NaOH until a precipitate crashed out of solution (pH ~5)--the solid was collected to give 4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol hydrobromide.

2) 7-(difluoromethoxy)-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline.

A 48 mL tube was charged with sodium 2-chloro-2,2-difluoroacetate (0.15 g, 1.0 mmol), 4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol hydrobromide (0.200 g, 0.44 mmol), cesium carbonate (0.43 g, 1.3 mmol), and DMF (1.7 ml, 22 mmol), flushed with argon, sealed, then placed in a 100°C oil bath for 5 hours. The reaction mixture was concentrated, then diluted with DCM and chloroform. This was washed with water, sat. $NaHCO_3$, and brine, then dried with $MgSO_4$, filtered, and concentrated to give a brown oil. This was purified by HPLC to give 7-(difluoromethoxy)-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline (0.025 g, 13% yield) as the formic acid salt. MS (ESI pos. ion) m/z: 424 (MH+). Calc'd exact mass for $C_{21}H_{15}F_2N_5O_3$: 423.



Example 435

N-((6-(1H-indazol-6-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine

a) 6-(3-((7-Methoxy-1,5-naphthyridin-4-ylamino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-1H-indazole-1-carboxylate. A tube was charged with N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine (0.250 g, 0.732 mmol), tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate (0.378 g, 1.10 mmol), PdCl2(dppf)-CH2Cl2Adduct (0.0597 g, 0.0732 mmol), potassium carbonate (0.303 g, 2.19 mmol), DMF (5.01 ml, 64.4 mmol), and water (1.16 ml, 64.4 mmol), flushed with argon, sealed, then placed in a 60°C oil bath for 6 hours. The reaction mixture was concentrated, then triturated with water to give a black solid. The material was used directly in the next step.

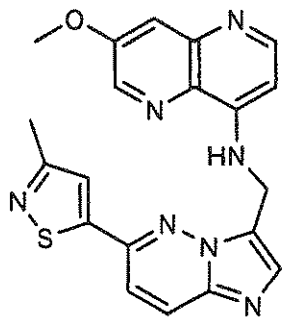
b) N-((6-(1H-indazol-6-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine. The title compound was prepared in the same manner as 7-methoxy-4-((6-(6-(piperazin-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methoxy)quinoline MS (ESI pos. ion) m/z: 424 (MH+). Calc'd exact mass for $C_{22}H_{17}N_9O$: 423.

4-bromo-1-(2,2,2-trifluoroethyl)-1H-pyrazole

A 250 mL RB flask was charged with 4-bromo-1H-pyrazole (2.00 g, 13.6 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.35 ml, 17.0 mmol), cesium carbonate (8.87 g, 27.2 mmol), and 1,4-dioxane (40.0 ml, 468 mmol), capped, and stirred at room temperature for 20 hours. The reaction mixture was filtered and the solid washed with dioxane; the filtrate was then concentrated to give 4-bromo-1-(2,2,2-trifluoroethyl)-1H-pyrazole (2.402 g, 77.1% yield) as a crude oil.

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole.

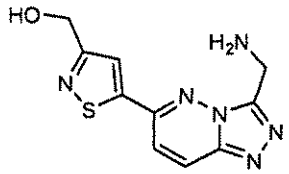
The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-(2,2,2-trifluoroethyl)-1H-pyrazole.



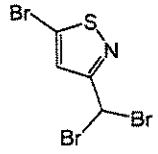
Example 436

7-methoxy-N-((6-(3-methylisothiazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine.

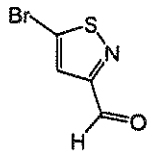
The title compound was prepared in the same manner as 7-Methoxy-N-((6-(3,4,5-trifluorophenyl)imidazo[1,2-b]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine. MS (ESI pos. ion) m/z: 404 (MH+). Calc'd exact mass for $C_{20}H_{17}N_7OS$: 403.



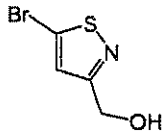
(5-(3-(aminomethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isothiazol-3-yl)methanol.



1) 5-bromo-3-(dibromomethyl) isothiazole. 5-Bromo-3-methylisothiazole (2.15 g, 12 mmol) was dissolved in dichloroethane (20 mL) then added N-bromosuccinimide (4.5 g, 25 mmol) and AIBN (0.50 g, 3.0 mmol). The reaction mixture was heated at 100 °C for 4 hours. Additional AIBN (0.50 g, 3.0 mmol) and bromine (0.062 ml, 1.2 mmol) were added to the mixture and continued heating at 100 °C for 4 hours. N-bromosuccinimide (4.5 g, 25 mmol) and AIBN (0.50 g, 3.0 mmol) were added then continued heating at 100 °C for 4 hours. Again, N-bromosuccinimide (4.5 g, 25 mmol) and AIBN (0.30 g, 1.8 mmol) were added and the mixture was heated at 100 °C for 4 hours. The reaction mixture was diluted with ethyl acetate and washed with water, saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and concentrated under vacuum. The sample was purified by flash chromatography eluting with 0-10% ethyl acetate/hexane to afford 5-bromo-3-(dibromomethyl)isothiazole (2.07 g, 51% yield) as a colorless liquid.

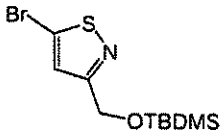


2) 5-bromoisothiazole-3-carbaldehyde. 5-Bromo-3-(dibromomethyl)isothiazole (1.00 g, 3.0 mmol) was dissolved in DME (10 mL) then added a solution of silver nitrate (0.56 g, 3.3 mmol) in water (1.6 mL). A white precipitate formed. The reaction mixture was heated at 100 °C for 1.5 hours. Additional silver nitrate (0.56 g, 3.3 mmol) in water (1.6 mL) was added and heating was continued at 100 °C for 2.5 hours. The reaction mixture was filtered through a pad of Celite washing with THF then ethyl acetate. The filtrate was concentrated under vacuum and the remaining oil was diluted with ethyl acetate. The organic layer was washed with water then dried over sodium sulfate and concentrated under vacuum to afford 5-bromoisothiazole-3-carbaldehyde (0.536 g, 94% yield) as alight yellow oil.



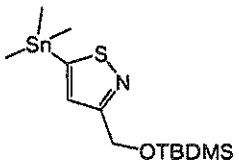
3)(5-bromoisothiazol-3-yl)methanol. 5-Bromoisothiazole-3-carbaldehyde (0.533 g, 2.8 mmol) was dissolved in ethanol (40 mL) then added sodium borohydride (0.11 g, 2.8 mmol). The reaction mixture was stirred at room temperature for 3 hours. Added more sodium borohydride (0.026 g, 0.69 mmol) and continued stirring at room temperature for 4.5 hours. Additional sodium borohydride (0.11 g, 2.8 mmol) was added once again and stirring was continued at room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride then concentrated under vacuum. The remaining aqueous layer was diluted with water then extracted with ethyl acetate (2x). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford (5-bromoisothiazol-3-yl)methanol (0.430 g, 80% yield) as an orange oil.

MS (ESI pos. ion) m/z: 194.0 and 196.0 (MH^+).

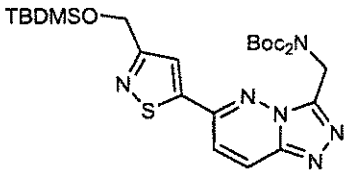


4) 5-bromo-3-((tert-butyldimethylsilyl oxy)methyl)isothiazole. (5-Bromoisothiazol-3-yl) methanol (0.380 g, 1.96 mmol) was dissolved in DMF (4 mL) then added tert-butyldimthylsilyl chloride (0.443 g, 2.94 mmol) and imidazole (0.400 g, 5.87 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was combined with previous reactions and concentrated under vacuum. The sample was purified by flash chromatography

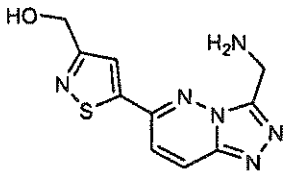
eluting with 0-15% ethyl acetate/hexane to afford 5-bromo-3-((tert-butyldimethylsilyloxy)methyl)isothiazole as a pale yellow liquid. MS (ESI pos. ion) m/z: 308.0 and 310.0 (MH^+).



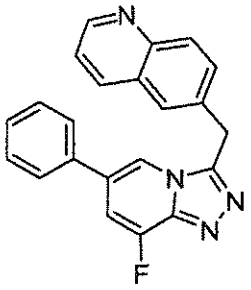
5) 3-((tert-butyldimethylsilyloxy) methyl)-5-(trimethylstannyl)isothiazole. 5-Bromo-3-((tert-butyldimethylsilyloxy)methyl)isothiazole (0.100 g, 0.324 mmol) was dissolved in THF (1 mL) then cooled to -78 °C and added 1.6 M n-BuLi in hexane (0.223 ml, 0.357 mmol) dropwise via syringe. The reaction mixture became yellow and stirring was continued at -78 °C for 45 minutes. 1M Trimethyltin chloride in THF (0.324 ml, 0.324 mmol) was added to the mixture dropwise via syringe. No color change was observed. Continued stirring at -78 °C for 1.5 hours. The reaction was quenched with saturated aqueous sodium bicarbonate at -78 °C then warmed to room temperature. The mixture was diluted with water then extracted with ether. The organic layer was dried over sodium sulfate and concentrated under vacuum to afford 3-((tert-butyldimethylsilyloxy)methyl)-5-(trimethylstannyl)isothiazole (0.121 g, 95.1% yield) as a light yellow liquid.



6) bis(1,1-dimethylethyl) (6-(3-((((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-5-isothiazolyl)[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate. Bis(1,1-dimethylethyl) (6-chloro[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate (0.200 g, 0.521 mmol) was suspended in dioxane (3 mL) then added 3-((tert-butyldimethylsilyloxy)methyl)-5-(trimethylstannyl)isothiazole (0.429 g, 1.09 mmol), xantphos (0.0301 g, 0.0521 mmol), palladium (II) acetate (0.00585 g, 0.0261 mmol), and water (0.0188 ml, 1.04 mmol). The reaction mixture was heated at 100 °C for 3 hours. The reaction mixture was concentrated under vacuum. The sample was purified by flash chromatography eluting with 0-100% ethyl acetate to afford bis(1,1-dimethylethyl) (6-(3-((((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-5-isothiazolyl)[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate (0.170 g, 56.6% yield) as a yellow oil. MS (ESI pos. ion) m/z: 577.2 (MH^+).



7) (5-(3-(aminomethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isothiazol-3-yl)methanol. Bis(1,1-dimethylethyl) (6-(3-((((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-5-isothiazolyl)[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate (0.170 g, 0.29 mmol) was dissolved in ethyl acetate (5 mL) then hydrochloric acid gas was bubbled through the mixture for approx. 5 minutes. A precipitate formed and stirring was continued at room temperature for 1.5 hours. The reaction was concentrated under vacuum then mostly redissolved in methanol (3.5 mL) and added ammonium hydroxide (0.052 ml, 1.3 mmol). The mixture was stirred at room temperature for 2 hours then concentrated under vacuum. The sample was purified by flash chromatography eluting with 50-100% 90:10:1 dichloromethane/methanol/NH4OH followed by 100% 90:10:1 dichloromethane/methanol/NH4OH to afford (5-(3-(aminomethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isothiazol-3-yl)methanol (0.066 g, 85% yield) as a white solid. MS (ESI pos. ion) m/z: 263.0 (MH^+).



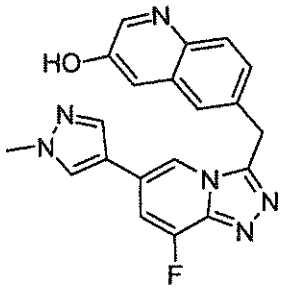
Example 437

6-((8-fluoro-6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline

1) 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline. A mixture of 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine (500 mg, 3095 μmol) and methyl 2-(quinolin-6-yl)acetate (600 mg, 2982 μmol) in HCl (conc., 600 μL, 7200 μmol) was heat at 100 °C for 20 min. The mixture was then heated in a microwave at 180 °C for 40 min. The mixture was quenched with NaOH (5 N, 1.5 mL) and the suspension was filtered and washed with H_2O. The resulting brown solid is mostly the desired product. The solid was then triturated with NaOH (5 N, 1 mL), filtered, and washed with H_2O. LCMS (ESI pos. ion): calc'd for $C_{16}H_{10}ClFN_4$: 312.0; found: 313.1 (M+1).

2) 6-((8-fluoro-6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline. A mixture of

$Pd(OAc)_2$ (6.46 mg, 28.8 μmol), potassium phosphate (367 mg, 1727 μmol), phenylboronic acid (211 mg, 1727 μmol), dicyclohexyl(2-(2,4,6-triisopropylcyclohexa-1,3-dienyl)phenyl)phosphine (27.6 mg, 57.6 μmol), and 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline (180 mg, 576 μmol) in dioxane (6 mL)-H_2O (2 mL) was heated to 100 °C under nitrogen for 20 h. The mixture was cooled to rt and partitioned between H_2O and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residual was purified on silica using MeOH in DCM (0-5%) to give a pink solid. This solid was triturated with hexane-EtOAc-DCM (hot) to give a brown solid (105 mg). LCMS (ESI pos. ion): calc'd for $C_{22}H_{15}FN_4$: 354.1; found: 355.2 (M+1).

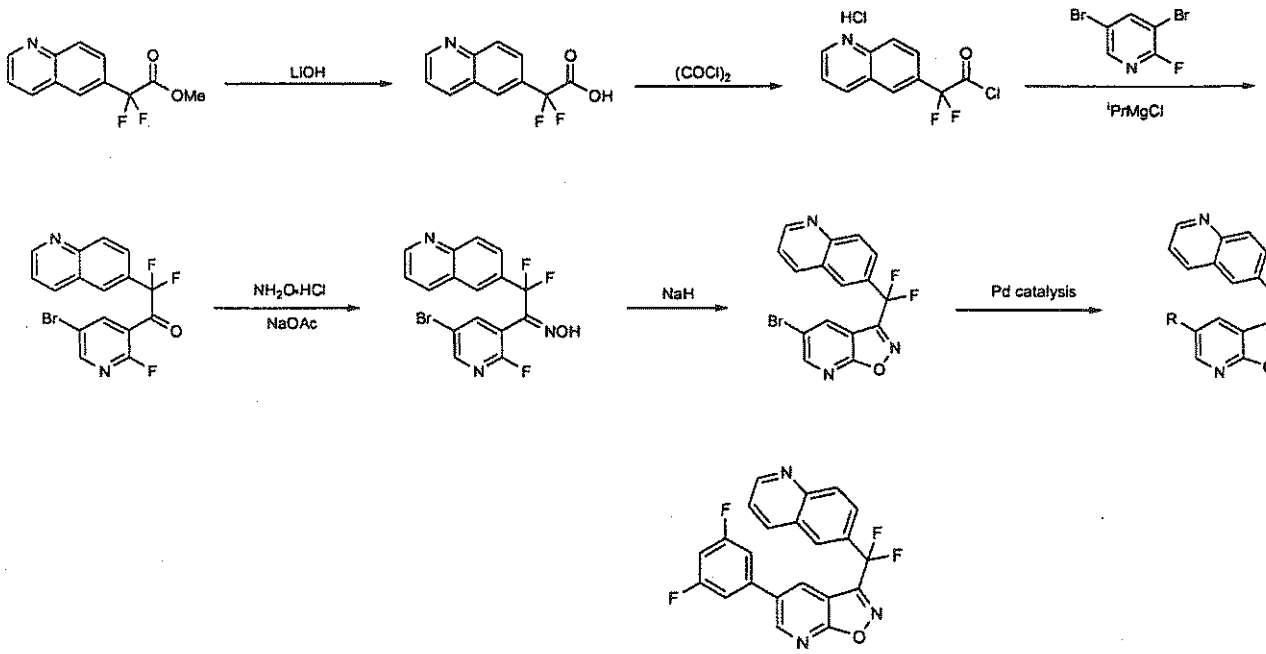


Example 438

6-((8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol.

A mixture of crude 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline (200 mg, 584 μmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (600 mg, 2884 μmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (24 mg, 29 μmol), and Na_2CO_3 (500 mg, 4717 μmol) in DME (7 mL)-H_2O (5 mL) was heated at 100 °C under nitrogen. After overnight, the sludge was treated with DMSO (10 mL) and filtered. The DMSO solution was purified on HPLC (10-60%/10min). The product fraction was concentrated to dryness with toluene. The solid was then triturated with MeOH-hexane (1:2) to give a brown powder (60 mg). LCMS (ESI pos. ion): calc'd for $C_{20}H_{15}FN_6O$: 374.1; found 375.1 (M+1).

General Method F



Example 439

6-((5-(3,5-difluorophenyl)isoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline

1) 2,2-difluoro-2-(quinolin-6-yl)acetic acid. To a solution of methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (2.0g, 8.4 mmol) in dioxane (4 mL) and water (12 mL) was added lithium hydroxide monohydrate (0.53 g, 12 mmol). After stirring at 50 °C for thirty minutes, the solution was brought to pH 4 with 2.0 N HCl. The solution was concentrated and dried on a lyophilizer overnight to yield the product as an orange solid. MS m/z = 224.0 [M+1

2) 2,2-difluoro-2-(quinolin-6-yl)acetyl chloride hydrochloride. To a suspension of 2,2-difluoro-2-(quinolin-6-yl)acetic acid (1.9 g, 8.4 mmol) in dichloromethane (16 mL) was added oxalyl chloride (7.4 mL, 84 mmol). The mixture was stirred at 45 °C for one hour. The suspension was filtered and the resulting filtrate concentrated to yield the product as an orange oil (1.8 g, 73% step 1 and 2 combined).

3) 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone. To a solution of 3,5-dibromo-2-fluoropyridine (3.1 g, 12 mmol) in anhydrous THF (12 mL) under argon was added isopropylmagnesium chloride (2.0 M in THF, 6.0 mL, 12 mmol). The solution was stirred at room temperature for ten minutes, then was added via cannula to a solution of 2,2-difluoro-2-(quinolin-6-yl)acetyl chloride hydrochloride (1.8 g, 6.1 mmol) in anhydrous THF (20 mL) at -78 °C. The solution was allowed to rise to -40 °C over one hour; then was stirred at 0 °C for one hour. The reaction was quenched with water and extracted with ethyl acetate; organic extracts were dried over magnesium sulfate and concentrated. Purification by MPLC

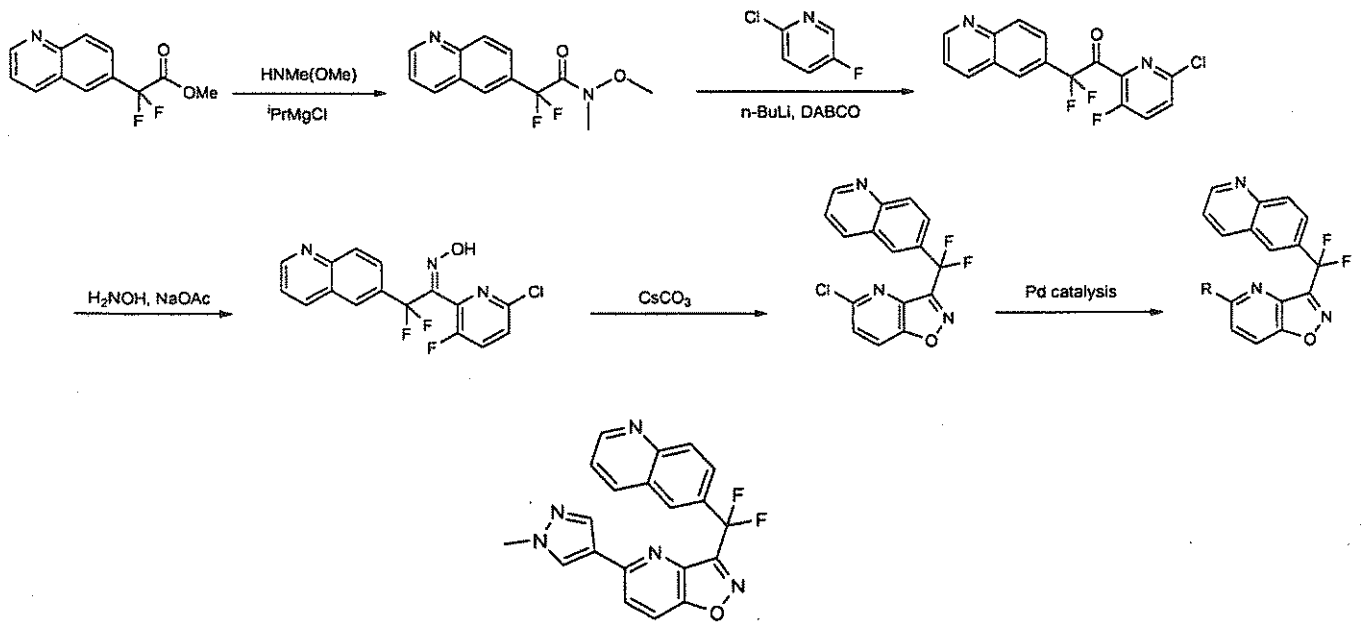
(eluted with a gradient of 20 to 80% ethyl acetate in hexanes) afforded the product as a tan solid (0.90 g, 38%).

4) 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime. To a pressure vessel was added hydroxylamine hydrochloride (1.6 g, 24 mmol), sodium acetate (2.9 g, 35 mmol) and 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone (0.90 g, 2.4 mmol) in acetic acid (20 mL). The suspension was sealed and stirred at 100 °C for fifteen minutes, then was concentrated, triturated with water and filtered. Purification of the resulting solid by MPLC (eluted with a gradient of 0-10% methanol in dichloromethane) afforded the product as a beige solid (0.59 g, 63%). MS m/z = 396.0 $[M+1]^+$

5) 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline. To a solution of 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime (0.59 g, 1.5 mmol) in anhydrous THF (10 mL) was added sodium hydride (0.090 g, 2.3 mmol) at 0 °C. After ten minutes, the solution was diluted with ethyl acetate and washed with water, organic extracts were dried over magnesium sulfate. Purification by MPLC (eluted with a gradient of 20-50% ethyl acetate in hexanes) afforded the product as a white solid (0.39g, 70%). MS m/z = 377.0 $[M+1]^+$ Calc'd for $C_{16}H_8BrF_2N_3O$: 376.2

6) 6-((5-(3,5-difluorophenyl)isoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline. To a pressure vessel was added $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.0076 g, 0.0093 mmol), cesium carbonate (0.13 g, 0.40 mmol), 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline (0.050 g, 0.13 mmol) and 3,5-difluorophenylboronic acid (0.031g, 0.020 mmol) in DMF (1.0 mL) water (0.25 mL). The vessel was purged with argon, sealed and stirred at 80 °C for two hours. The mixture was concentrated, triturated with water an filtered; purification of the resulting precipitate by MPLC (eluted with a gradient of 20 to 50 % ethyl acetate in hexanes afforded the product as a white solid (27 mg, 53%).

General Method G



Example 440

6-(difluoro(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[4,5-b]pyridin-3-yl)methyl)quinoline

1) 2,2-difluoro-N-methoxy-N-methyl-2-(quinolin-6-yl)acetamide. To a solution of N-methoxymethanamine hydrochloride (3.7 g, 38 mmol) and methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (6.0 g, 25 mmol) in anhydrous THF (30 mL) was added isopropylmagnesium chloride (2.0 M, 38 mL, 76 mmol) at -20 °C. After thirty minutes the reaction was quenched with saturated ammonium chloride and extracted with diethyl ether; organic extracts were dried over magnesium sulfate. Purification by MPLC (eluted with a gradient of 10 to 70 % ethyl acetate in hexanes) afforded the product as an orange solid. MS m/z = 267.2 $[M+1]^+$.

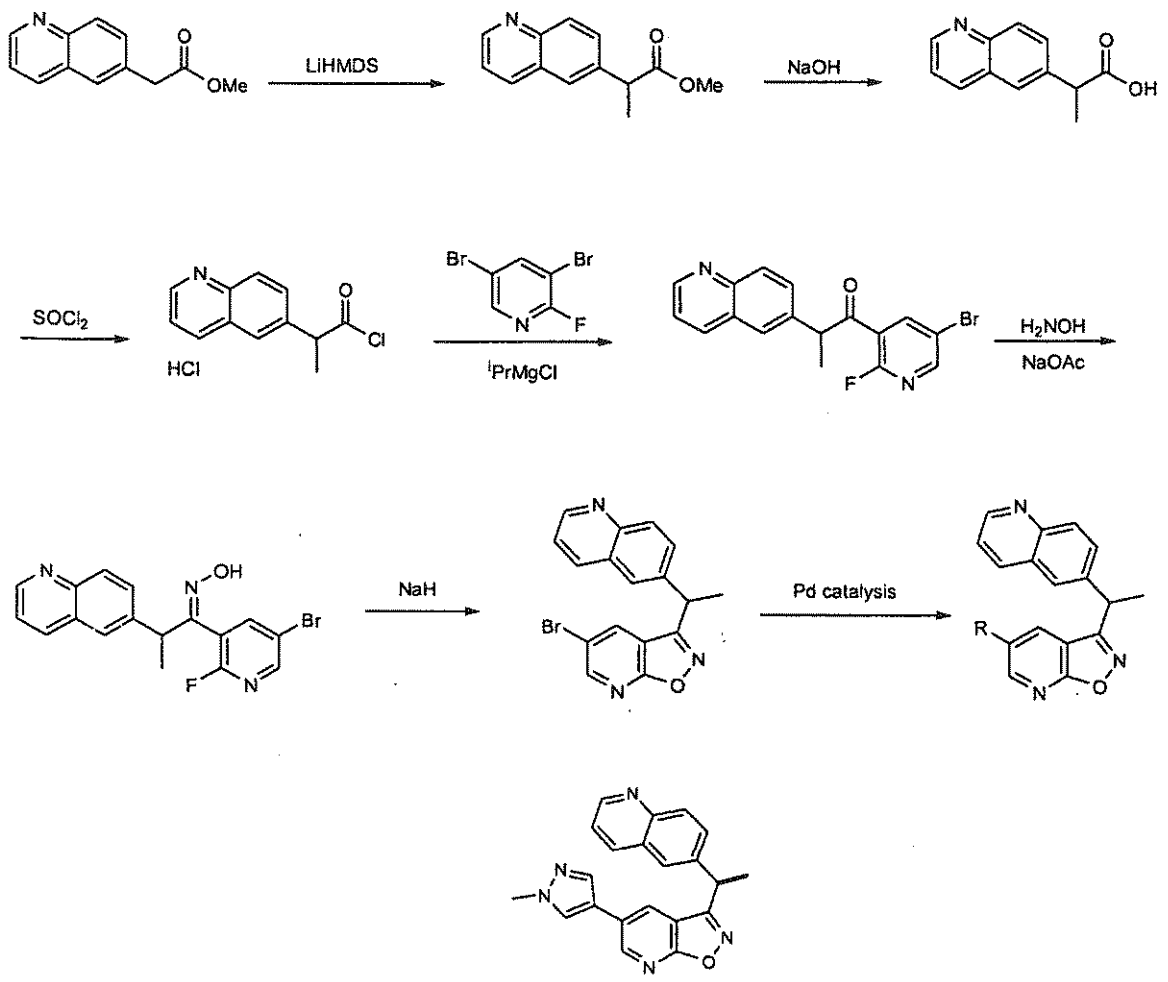
2) 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone. n-Butyllithium (2.5M in hexanes, 3.70 ml, 9.25 mmol) was added to a stirred solution of DABCO (1.04 g, 9.25 mmol) in Et_2O (46 mL) at -78°C. The reaction mixture was stirred 1h at -20°C. and then cooled again at -78°C. 2-Chloro-5-fluoropyridine (0.939 ml, 9.25 mmol) in Et_2O (5 mL) was added. Stirring was continued at -78°C for 1h. 2,2-Difluoro-N-methoxy-N-methyl-2-(quinolin-6-yl)acetamide (2.24 g, 8.41 mmol) in Et_2O (20 mL) was added by cannula. The reaction mixture was stirred at -78°C for 70min. The cooling bath was replaced by an ice/water bath. After 10 min of stirring at 0°C , the reaction mixture was quenched with water. The water layer was extracted with EtOAc and DCM/MeOH(9/1). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by MPLC (hexanes/EtOAc: 100/0 to 40/60) afforded the title compound (2.27g, 80% yield).

3) 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime. To a pressure vessel was added 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone (1.0 g, 3.0 mmol), sodium acetate (3.7 g, 45 mmol) and hydroxylamine hydrochloride (2.1 g, 30 mmol) in acetic acid (15 mL). The vessel was sealed and the suspension was stirred at 100 °C for twenty minutes. Following concentration and trituration with water, a white precipitate was collected via filtration. Purification of the solid by MPLC (eluted with 0-10% methanol in dichloromethane) afforded the product as a white solid (0.85 g, 82%) MS m/z = 352.0 $[M+1]^+$.

4) 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline. To a pressure vessel was added 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime (0.050 g, 0.14 mmol) and cesium carbonate (0.14 g, 0.43 mmol) in anhydrous DMF (1 mL). After stirring at 80 °C for 30 minutes, the solution was diluted with ethyl acetate and washed with water. Organic extracts were dried over magnesium sulfate and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) to yield the product as a white solid (35 mg, 74%) MS m/z = 332.2 $[M+1]^+$. Calc'd for C16H8ClF2N3O: 331.7.

5) 6-(difluoro(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[4,5-b]pyridin-3-yl)methyl)quinoline. To a pressure vessel was added 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline) (0.10 g, 0.30 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.012 g, 0.015 mmol), cesium carbonate (0.29 g, 0.90 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.094 g, 0.45 mmol) in DMF (2 mL) and water (0.5 mL). The vessel was purged with argon, sealed and stirred at 80 °C for forty minutes. The mixture was diluted with ethyl acetate and washed with water, organic extracts were dried over magnesium sulfate. Purification by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) afforded the product as a light yellow solid (45 mg, 40%). MS m/z = 378.2 $[M+1]^+$ Calc'd for $C_{20}H_{13}F_2N_5O$: 377.3.

General Method H



Example 441

6-((R)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

1) Methyl 2-(quinolin-6-yl)propanoate. To a solution of methyl 2-(quinoline-6-yl)acetate (7.0 g, 35 mmol) in anhydrous THF (70 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 35 mL, 35 mmol) and solution of methyl iodide (2.2 mL, 35 mmol) in anhydrous THF (1mL) at -78 °C. The dry ice in acetone bath was removed and the mixture was stirred for 35 minutes, then was quenched with saturated ammonium chloride (30 mL), diluted with ethyl acetate and washed with saturated sodium bicarbonate. Organic extracts were dried over magnesium sulfate and purified via MPLC (eluted with a gradient of 10 to 30% ethyl acetate in hexanes) to yield the product as a light yellow oil (6.5 g, 87%).

2) 2-(quinolin-6-yl)propanoic acid. To a solution of methyl 2-(quinolin-6-yl)propanoate (1.4 g, 6.5 mmol) in methanol (7 mL) and water (1.5 mL) was added sodium hydroxide (6 N, 2.7 mL, 16 mmol) and the solution was stirred at 50 °C for one hour. The solution was concentrated, brought to pH 4 with 2.0 N HCl and the product was isolated via filtration as a white solid (0.94 g, 72%).

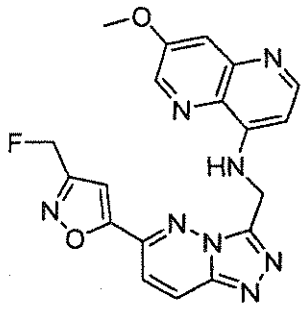
3) 2-(quinolin-6-yl)propanoyl chloride hydrochloride. To a suspension of 2-(quinolin-6-yl)propanoic acid (0.73 g, 3.6 mmol) in anhydrous dichloromethane (15 mL) was added thionyl chloride (1.3 mL, 18 mmol) and the solution was stirred at room temperature for ten minutes. The solution was concentrated to yield the product as an orange solid.

4) 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one. To a solution of 3,5-dibromo-2-fluoropyridine (2.4 g, 9.3 mmol) in anhydrous THF (10 mL) was added isopropylmagnesium chloride (2.0 M in THF, 4.7 mL, 9.3 mmol) and stirred at room temperature for ten minutes. The solution was added via cannula to a solution of 2-(quinolin-6-yl)propanoyl chloride hydrochloride (0.79 g, 3.1 mmol) in anhydrous THF (10 mL) at -78 °C and the combined reaction mixture was allowed to rise to -40 °C over one hour. The mixture was stirred at -40 °C for an additional 90 minutes, then was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. Organic extracts were dried over magnesium sulfate and purified via MPLC (eluted with a gradient of 10-80% ethyl acetate in hexanes) to yield the product as a yellow oil (0.60 g, 54%).

5) 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one oxime. To a pressure vial was added sodium acetate (2.0 g, 24 mmol), hydroxylamine hydrochloride (1.1 g, 16 mmol) and 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one (0.58 g, 1.6 mmol) in acetic acid (10 mL). The vial was sealed and stirred at 100 °C for one hour, then was concentrated, diluted with ethyl acetate and washed with water. Organic extracts were concentrated and purified by MPLC (eluted with 0-10% methanol in dichloromethane) to yield the product as a tan oil (0.50 g, 83%).

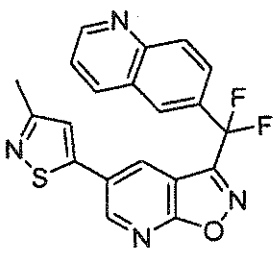
6) 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. To a solution of 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one oxime (0.58 g, 1.6 mmol) in THF (15 mL) was added sodium hydride (60% in mineral oil, 0.093, 2.3 mmol) at 0 °C. The solution was stirred at 0 °C for ten minutes, then was diluted with ethyl acetate and washed with water. Organic extracts were concentrated and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) to yield the product as a colorless oil (0.10 g, 19%). MS m/z = 354.0 $[M+1]^+$. Calc'd for $C_{17}H_{12}BrN_3O$: 354.2

7) 6-((R)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. To a pressure vial was added 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline (0.09 g, 0.25 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.010 g, 0.013 mmol), cesium carbonate (0.25 g, 0.76 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.079 g, 0.38 mmol) in DMF (2.5 mL) and water (0.5 mL). The vessel was flushed with argon, sealed and stirred at 90 °C for one hour. The mixture was concentrated, triturated in water and a brown solid was collected via filtration. Purification by MPLC (eluted with a gradient of 10 to 50% ethyl acetate) afforded a racemic mixture of the product. The desired enantiomer (>99% ee) was obtained via SFC. MS m/z = 356.2 $[M+1]^+$ Calc'd for $C_{21}H_{17}N_5O$: 355.4



Example 442

N-((6-(3-(fluoromethyl)isoxazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine: To a suspension of (5-(3-((7-methoxy-1,5-naphthyridin-4-ylamino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isoxazol-3-yl)methanol (0.080 g, 0.20 mmol) in anhydrous dichloromethane (3 mL) was added deoxofluor (0.10 mL, 0.060 mmol) under argon at 0 °C. The solution was brought to room temperature over one hour and stirred three additional hours. The reaction was quenched with saturated sodium bicarbonate and stirred for 15 minutes; a brown gum was collected by filtration. Purification via MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) afforded the product as an off-white solid (9.0 mg, 11%). MS m/z = 407.2 $[M+1]^+$. Calc'd for $C_{19}H_{15}FN_8O_2$: 406.4

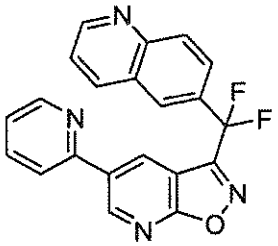
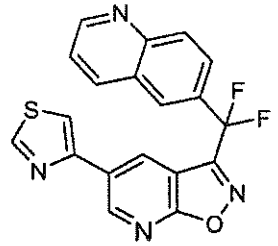
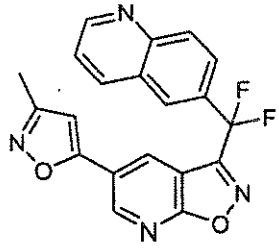
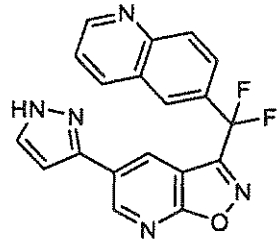


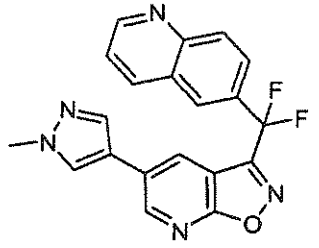
Example 443

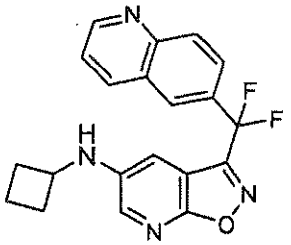
6-(difluoro(5-(3-methylisothiazol-5-yl)isoxazolo[5,4-b]pyridin-3-yl)methyl)quinoline

To a pressure vial was added 2-(dicyclohexylphosphino)biphenyl (9.3 mg, 0.013 mmol), 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.27 mmol), 3-methyl-5-(trimethylstannyl)isothiazole (0.14g, 0.53 mmol) and $Pd_2(dba)_3$ (12 mg, 0.013 mmol) in anhydrous DMF (5 mL). The vessel was purged with argon, sealed and stirred at 80 °C for ninety minutes. The mixture was concentrated and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) to yield the product as a light yellow solid. MS m/z = 395.0 $[M+1]^+$ Calc'd for $C_{20}H_{12}F_2N_4OS$: 394.4.

The following example compounds 444-448 were prepared using a method similar to 6-(difluoro(5-(3-methylisothiazol-5-yl)isoxazolo[5,4-b]pyridin-3-yl)methyl)quinoline:

Ex	Structure	MW	Mass Found
444		374	375
445		380	381
446		378	379
447		363	364

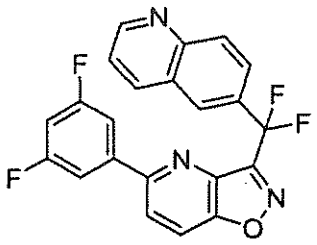
448		377	378



Example 449

N-cyclobutyl-3-(difluoro(quinolin-6-yl)methyl)isoxazolo[5,4-b]pyridin-5-amine

To a pressure vial was added sodium tert-butoxide (38 mg, 0.40 mmol), xantphos (0.12 g, 0.20 mmol), $Pd_2(dba)_3$ (61 mg, 0.066 mmol), 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.27 mmol), and cyclobutanamine (0.025 mL, 0.29 mmol) in toluene (3 mL). The mixture was stirred at 80 °C for two hours then was diluted with dichloromethane and filtered through celite. Purification of the filtrate by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) afforded the product as a yellow oil (5.1 mg, 5%). MS m/z = 367.0 $[M+1]^+$ Calc'd for $C_{20}H_{16}F_2N_4O$: 366.4

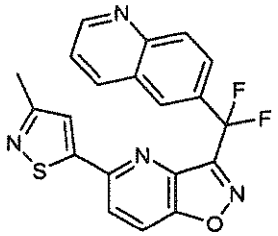


Example 450

6-((5-(3,5-difluorophenyl)isoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline

To a pressure vessel was added cesium carbonate (0.61 g, 1.9 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (26 mg, 0.031 mmol), 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime (0.26 g, 0.63 mmol) and 3,5-difluorophenylboronic acid (0.15 g, 0.94 mmol) in anhydrous DMF (5 mL) and water (1mL). The mixture flushed with argon, sealed and stirred at 80 °C for one hour. The suspension was concentrated, triturated with water and filtered to afford a tan solid, purification by MPLC (eluted with a gradient of 20 to 50% ethyl

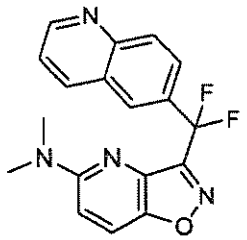
acetate in hexanes) afforded the product as a white solid (23 mg, 9%). MS m/z = 410.0 $[M+1]^+$ Calc'd for $C_{22}H_{11}F_4N_3O$: 409.3.



Example 451

6-(difluoro(5-(3-methylisothiazol-5-yl)isoxazolo[4,5-b]pyridin-3-yl)methyl)quinoline

To a solution of 5-bromo-3-methylisothiazole (0.19 g, 1.1 mmol) in anhydrous THF (3 mL) was added isopropylmagnesium lithium chloride (1.0 M in THF, 1.5 mL, 1.5 mmol) at -40 °C. The mixture was stirred at -40 °C for twenty minutes followed by the addition of zinc chloride (0.5 M in THF, 3.1 mL, 1.6 mmol). The mixture was brought to room temperature and stirred for thirty minutes followed by the addition of Q-Phos (0.12 g, 0.17 mmol), $Pd_2(dba)_3$ (0.097 g, 0.110 mmol), 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.30 mmol), and anhydrous dimethylacetamide (3.5 mL). The mixture was stirred at 50 °C for ninety minutes then was diluted with ethyl acetate and washed with water. Organic extracts were dried over magnesium sulfate and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes), then purified by HPLC (eluted with a gradient of 15 to 90% acetonitrile in water) to afford the product as a white solid (4.2 mg, 3%). MS m/z = 395.2 $[M+1]^+$ Calc'd for $C_{23}H_{15}F_2N_3O$: 394.4.

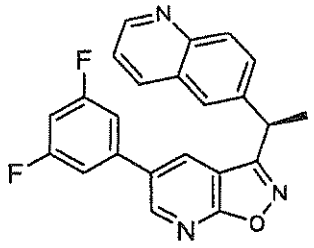
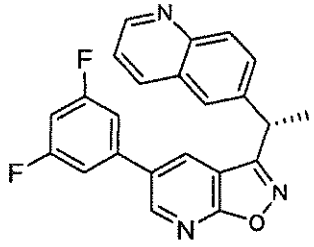


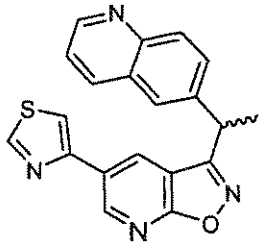
Example 452

3-(difluoro(quinolin-6-yl)methyl)-N,N-dimethylisoxazolo[4,5-b]pyridin-5-amine

To a microwave vial was added dimethylamine (2.0 M in THF, 0.75 mL, 1.5 mmol) and , 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.30 mmol) in ethanol (3 mL). The mixture was stirred at 140 ° under microwave irradiation for two hours then was concentrated and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate

in hexanes) to yield the product as a light yellow solid (87 mg, 85%). MS m/z = 341.2 $[M+1]^+$ Calc'd for $C_{18}H_{14}F_2N_4O$: 340.3.

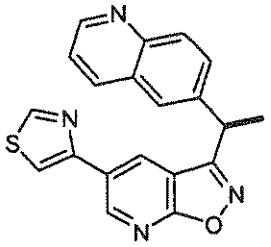
Ex	Structure	MW	Mass Found	Method
453		387	388	H
454		387	388	H



Example 455

6-(1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

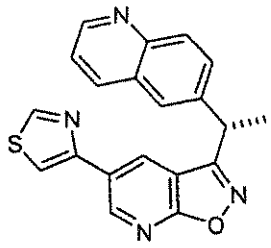
To a pressure vessel was added 2-(dicyclohexylphosphino)biphenyl (12 mg, 0.42 mmol), 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline (0.10 g, 0.28 mmol), and 4-(tributylstannyl)thiazole (0.16 g, 0.42 mmol) in anhydrous DMF (3 mL). The vial was flushed with argon, sealed and stirred at 90 °C for two hours. The mixture was concentrated and purified by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) to afford the product as an off-white solid. MS m/z = 359.0 $[M+1]^+$ Calc'd for $C_{20}H_{14}N_4OS$: 358.4.



Example 456

6-((R)-1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

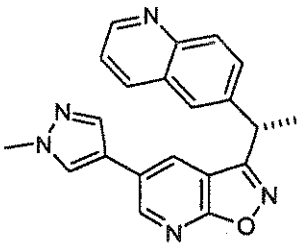
To a pressure vessel was added 2-(dicyclohexylphosphino)biphenyl (12 mg, 0.42 mmol), 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline (0.10 g, 0.28 mmol), 4-(tributylstannyl)thiazole (0.16 g, 0.42 mmol) in anhydrous DMF (3 mL). The vial was flushed with argon, sealed and stirred at 90 °C for two hours. The mixture was concentrated and purified by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) to yield the racemic product as an off-white solid. The desired enantiomer (>99% ee) was obtained via SFC. MS m/z = 359.0 $[M+1]^+$ Calc'd for $C_{20}H_{14}N_4OS$: 358.4



Example 457

6-((S)-1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

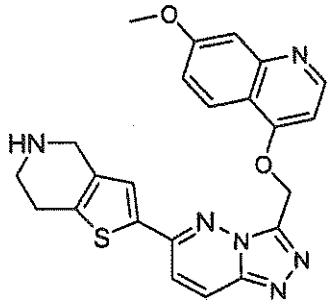
Prepared by a method similar to 6-((R)-1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. MS m/z = 359.0 $[M+1]^+$ Calc'd for $C_{20}H_{14}N_4OS$: 358.4.



Example 458

6-((S)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

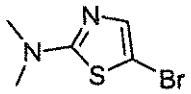
Prepared by a method similar to 6-((R)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. MS m/z = 356.2 $[M+1]^+$ Calc'd for $C_{21}H_{17}N_5O$: 355.4



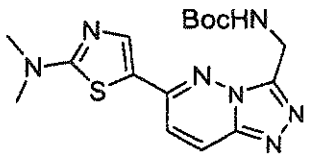
Example 459

7-methoxy-4-((6-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methoxy)quinoline

To a solution of tert-butyl 2-(3-((7-methoxyquinolin-4-yloxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (0.27 g, 0.50 mmol) (prepared according to general method A) was added trifluoroacetic acid (0.77 mL, 10 mmol). The mixture was stirred at room temperature for 90 minutes, then was concentrated, taken up in 2.0 M ammonia in methanol and purified by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) to yield the product as a pink solid. MS m/z = 445.0 $[M+1]^+$ Calc'd for $C_{23}H_{20}N_6O_2S$: 444.51.



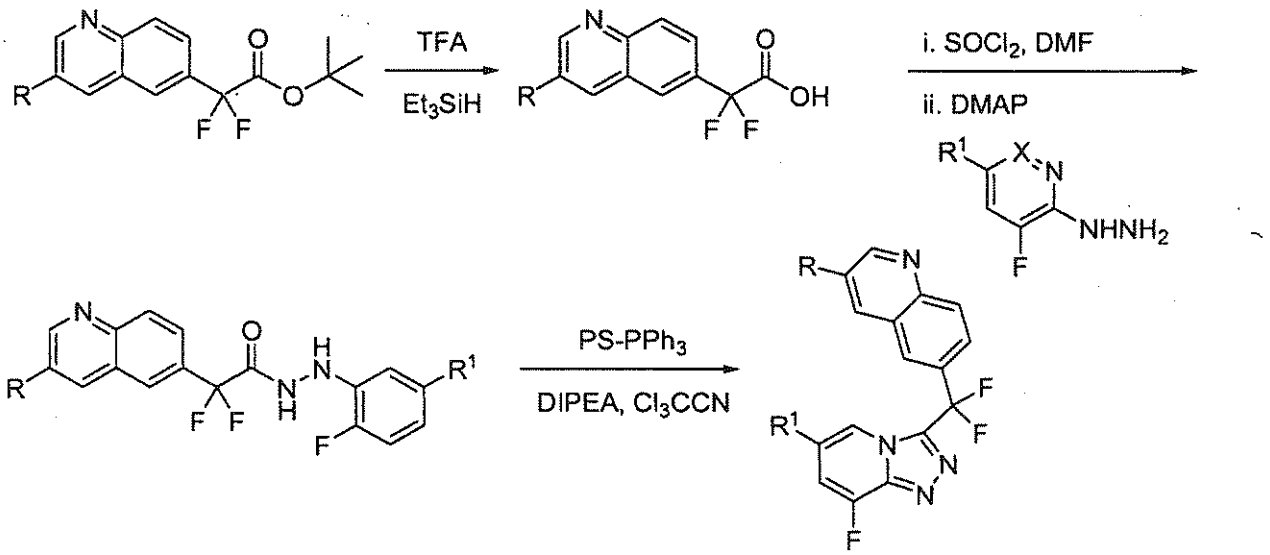
5-bromo-N,N-dimethylthiazol-2-amine: To a microwave vial was added N-ethyl-N-isopropylpropan-2-amine (0.72 mL, 4.1 mmol), 2,5-dibromothiazole (1.00 g, 4.1 mmol) and dimethylamine (40% in water, 0.52 mL, 4.1 mmol) in ethanol (10 mL). The vial was sealed and stirred at 140 °C under microwave irradiation for one hour, then was concentrated and purified by MPLC (eluted with a gradient of 0-50% ethyl acetate in hexanes) to yield the product as a white, crystalline solid (0.25 g, 29%).

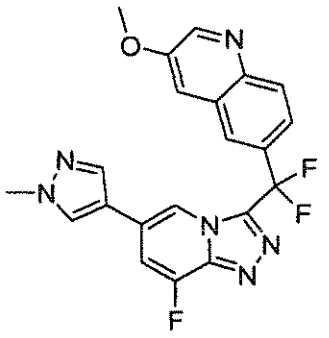


tert-butyl (6-(2-(dimethylamino)thiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate: To a solution of 5-bromo-N,N-dimethylthiazol-2-amine (0.73 g, 3.53 mmol) in anhydrous THF (9 mL) was added isopropylmagnesium lithium chloride (1.0 M in THF, 4.8 mL, 4.8 mmol) at -40 °C. The solution was stirred for twenty minutes followed by

the dropwise addition of zinc chloride (0.5 M in THF, 10 mL, 5.2 mmol). The mixture was brought to room temperature and stirred for thirty minutes followed by the addition of dimethylacetamide (12 mL), $Pd_2(dba)_3$, (0.32 g, 0.35 mmol), Q-Phos (0.34 g, 0.56 mmol), and tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.29 g, 1.0 mmol). The mixture was stirred at 50 ° for two hours then was quenched with saturated ammonium chloride and purified by MPLC chromatography (eluted with a gradient of 0 to 10% (1:10:90 NH_4OH:MeOH:DCM) in DCM) to yield the product as a light orange solid (0.27 g, 71%).

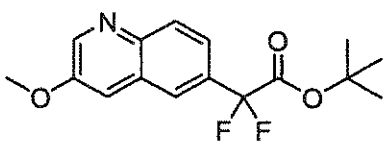
General Method I



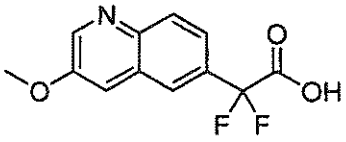


Example 460

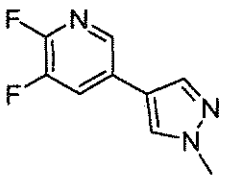
6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline



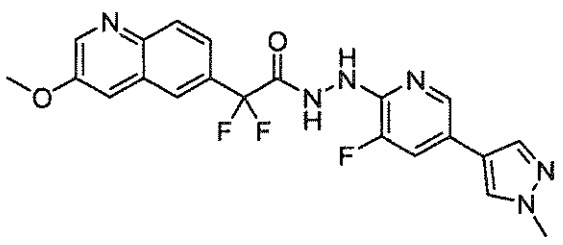
1) tert-butyl 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetate. The title compound was made from tert-butyl 2-(3-methoxyquinolin-6-yl)acetate in a similar fashion to the procedure reported for the synthesis of methyl 2,2-difluoro-2-(quinolin-6-yl)acetate.



2) 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid. A 200 mL round bottom flask was charged with tert-butyl 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetate (5.06 g, 16 mmol) then CH_2Cl_2, then trifluoroacetic acid (16 ml, 213 mmol) followed by triethylsilane (6.5 ml, 41 mmol). The solution was maintained at rt for 24 h until LCMS showed disappearance of starting material. The solution was concentrated and was subjected to high vacuum for 40 h to give 4.1 g (99% yield) of 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid as a brown solid. The material was of sufficient purity for use in subsequent steps.

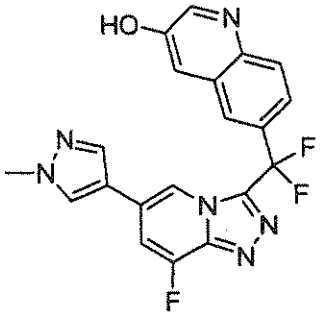


3) 2,3-difluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridine. A sealable flask was charged with 5-chloro-2,3-difluoropyridine (1.541 g, 10.3 mmol), palladium(ii) acetate (0.116 g, 0.515 mmol), potassium phosphate tribasic (6.56 g, 30.9 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.57 g, 12.4 mmol), and X-Phos (0.491 g, 1.03 mmol). The flask was sealed with a septum cap, then dioxane (20 mL) and H2O (2 mL) were added. The resulting mixture was sparged with N_2 for 10 min, and then heated at 100 °C for 2 h. The solution was cooled to rt and then concentrated and purified by flash chromatography using eluent 99:1 Hexanes : EtOAc to 60:40 Hexanes : EtOAc gradient to afford 2,3-difluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridine (1.78 g, 88.5% yield) as a colorless film. LRMS (ESI) *m/z* calcd for $C_9H_7F_2N_3$ (M+H) 197.1, found 197.4.



4) 2,2-difluoro-N'-(2-fluoro-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-2-(3-methoxyquinolin-6-yl)acetohydrazide. A round bottom flask was charged with 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid (389 mg, 1536 μmol) and DMF (8 mL). The solution was cooled to 0 C, thionyl chloride (224 μl, 3073 μmol), was added and the resulting solution was maintained 1 h at 0 °C. Then, triethylamine (641 μl, 4609 μmol)was added via syringe, followed by 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (382 mg, 1844 μmol) and 4-(dimethylamino)pyridine (18.8 mg, 154 μmol); both added as solids. The heterogeneous solution was stirred at 0 °C for 1 h, then allowed to warm to rt and stir for 18 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and the resulting mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were concentrated (heating to 50 °C) and the residue purified by SiO_2 chromatography solvent system: CH_2Cl_2:MeOH 99%:1% gradient 90:10 CH_2Cl_2 to yield 2,2-difluoro-N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(3-methoxyquinolin-6-yl)acetohydrazide (225 mg, 33.1% yield) as a brown amorphous solid.

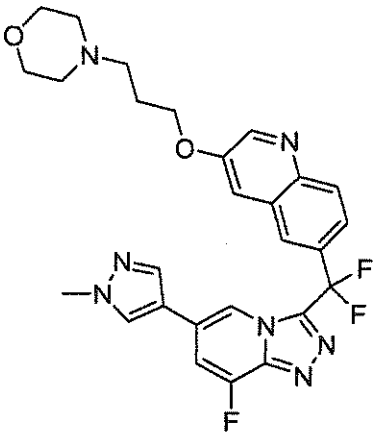
5) 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline. A sealable microwave vial was charged with 2,2-difluoro-N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(3-methoxyquinolin-6-yl)acetohydrazide (225 mg, 509 μmol) and polymer supported triphenylphosphine (2.3 mmol/g, 221 mg, 509 μmol). The flask was sealed and dichloroethane (4 mL) was added followed by diisopropylethylamine (89 μl, 509 μmol) and 2,2,2-trichloroacetonitrile (127 μl, 1271 μmol). The resulting mixture was irradiated in a microwave (Biotage Initiator) at 150 °C for 40 min. The reaction mixture was filtered and the filter cake was washed with CH_2Cl_2 (15 mL) and MeOH (10 mL). The filtrate was concentrated *in vacuo* and the resulting crude residue was purified by MPLC using 100% CH_2Cl_2 to 98:2 CH_2Cl_2 : MeOH to afford 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline (94 mg, 44% yield) as a tan amorphous solid. LRMS (ESI) *m/z* calcd for $C_{21}H_{16}F_3N_6O$ (M+H) 425.1, found 425.4.



Example 461

6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol.

To a flask charged with 3-(benzyloxy)-6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline (10 mg, 20 μmol) was added trifluoroacetic acid (1.5 mL, 20 mmol). The resulting solution was heated at 65 °C for 18 h. The solution was concentrated for purification by MPLC using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to afford 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol (3.6 mg, 44% yield) as a colorless solid. LRMS (ESI) *m/z* calcd for $C_{20}H_{14}F_3N_6O$ (M+H) 411.1, found 411.3.

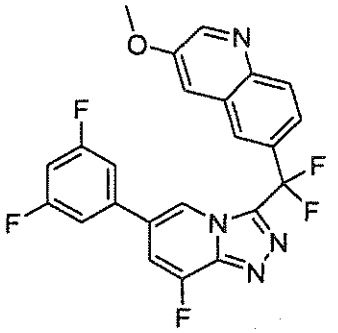


Example 462

6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-(3-morpholinopropoxy)quinoline.

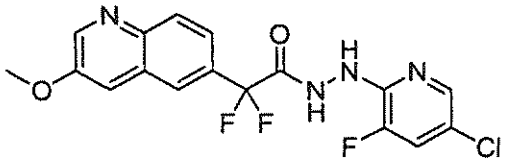
To a flask charged with 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol (17.3 mg, 42 μmol), was added triphenylphosphine (55 mg, 211 μmol), THF (1 mL), and 4-(3-hydroxypropyl)-morpholine,95% (31 μl, 211 μmol). The mixture was placed under N_2 and cooled to 0 °C. Di-tert-butyl azodicarboxylate (49 mg, 211 μmol) was added as a solid in a single portion and the solution was allowed to warm to rt and was maintained for 48 h. The solution was concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2

and absorbed onto a 5 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (40 g) using 99:1 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to afford 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-(3-morpholinopropoxy)quinoline (7.5 mg, 33% yield) as a colorless solid.; . LRMS (ESI) *m/z* calcd for $C_{27}H_{27}F_3N_7O_2$ (M+H) 538.2, found 538.2.

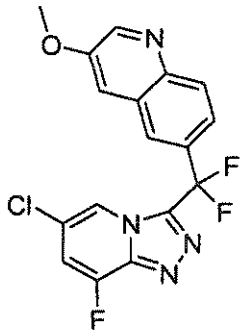


Example 463

6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline

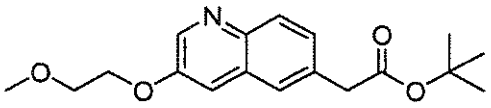


a) N'-(5-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetohydrazide. This compound was assembled from 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid and 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine according to General Method I. LRMS (ESI) *m/z* calcd for $C_{17}H_{13}ClF_3N_4O_2S$ (M+H) 397.1, found 397.2.



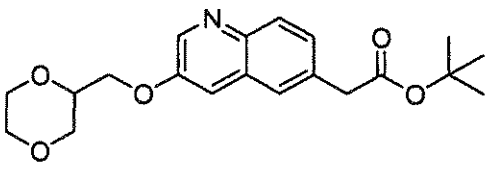
b) 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline. This compound was made from N'-(5-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetohydrazide according to General Method I. LRMS (ESI) *m/z* calcd for $C_{17}H_{11}ClF_3N_4O$ (M+H) 379.1, found 379.2.

c) 6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline. A sealable microwave vial was charged with 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline (342.05mg, 903 μmol), palladium(II) acetate (30 mg, 135 μmol), potassium phosphate (575 mg, 2709 μmol), 3,5-difluorophenylboronic acid (285 mg, 1806 μmol), and X-Phos (129 mg, 271 μmol). The tube was sealed, and flushed with N_2. Dioxane (9 mL), then H_2O (1 mL) were added and the mixture was sparged with N_2 for 10 min, then heated at 100 °C for 24 h. The mixture was cooled to rt and concentrated absorbed onto a 5 g loading cartridge for MPLC purification using a 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to give 6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline (72 mg, 17% yield). LRMS (ESI) *m/z* calcd for $C_{23}H_{14}F_5N_4O$ (M+H) 457.1, found 457.0.



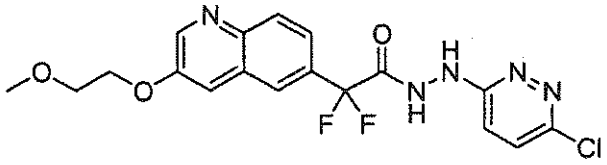
tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate.

A flask was charged with tert-butyl 2-(3-hydroxyquinolin-6-yl)acetate (581.04 mg, 2.241 mmol) and triphenylphosphine (1.175 g, 4.482 mmol) then sealed with a septum and an placed under N_2. Benzene (10 mL) was added, followed by 2-methoxyethanol (0.8838 ml, 11.20 mmol). The heterogeneous solution was cooled to 0 °C, and di-tert-butyl azodicarboxylate (1.032 g, 4.482 mmol) was added as a solid in a single portion. The solution was allowed to warm to rt and maintained 20 h. The solution was then partitioned between saturated aqueous. NH_4Cl, and the layers separated. The aqueous layer was extracted with EtOAc (2x50 mL), and the combined organic layers were washed with brine, dried (MgSO4), and concentrated *in vacuo*. The resulting residue was purified by MPLC (Teledine Isco combiFlash Companion), 80 g SiO_2, solvent system: 90:10 hexanes:EtOAc gradient to 50:50 hexanes:EtOAc to give tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate (585. 2 mg, 82% yield). LRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_4$ (M+H) 318.2, found 318.3.



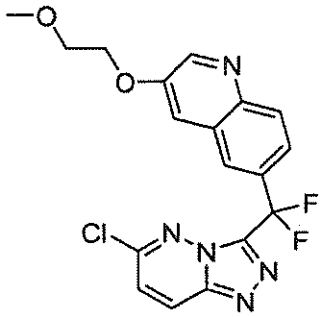
tert-butyl 2-(3-((1,4-dioxan-2-yl)methoxy)quinolin-6-yl)acetate (racemate).

The title compound was assembled from tert-butyl 2-(3-hydroxyquinolin-6-yl)acetate and (1,4-dioxan-2-yl)methanol according to the procedure described for tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate.



N'-(6-chloropyridazin-3-yl)-2,2-difluoro-2-(3-(2-methoxyethoxy)quinolin-6-yl)acetohydrazide.

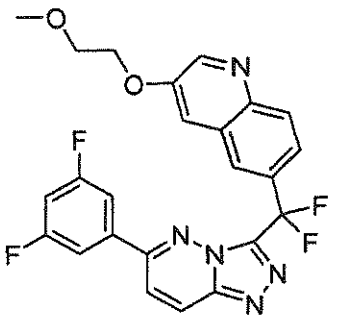
The title compound was assembled from 1-(6-chloropyridazin-3-yl)hydrazine and tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate as described in General Method I. LRMS (ESI) *m/z* calcd for $C_{18}H_{17}ClF_2N_5O_3$ (M+H) 424.1, found 424.2.



Example 464

6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline.

A sealable microwave vial was charged with N'-(6-chloropyridazin-3-yl)-2,2-difluoro-2-(3-(2-methoxyethoxy)quinolin-6-yl)acetohydrazide (46.98mg, 111 μmol), 1,2-dimethoxyethane (1.5 mL), and 1 drop of conc. HCl. The vial was sealed and heated at 130 °C for 40 min. The solution was concentrated and purified by MPLC (Teledine Isco combiFlash Companion). The residue was taken up in minimal CH_2Cl_2 and absorbed onto a 5 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (12 g) using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH to afford 6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline (25.3mg, 56.2% yield) as a colorless solid. LRMS (ESI) *m/z* calcd for $C_{18}H_{15}ClF_2N_5O_2$ (M+H) 406.1, found 406.2.

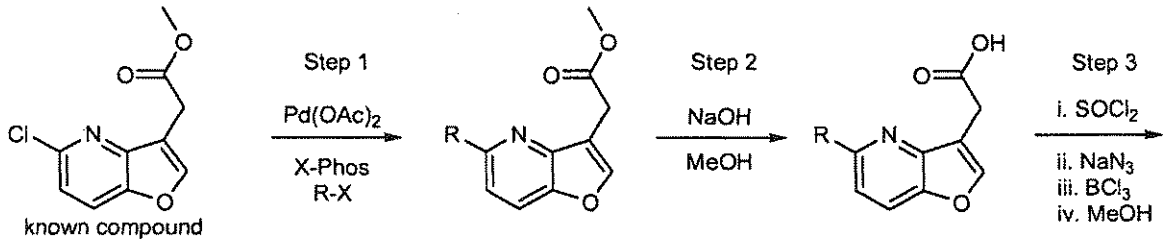


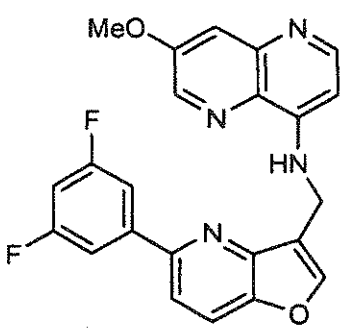
Example 465

6-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline.

The title compound was synthesized from 6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline and 3,5-difluorophenylboronic acid in a similar manner as that described for 6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline. LRMS (ESI) *m/z* calcd for $C_{24}H_{18}F_4N_5O_2$ (M+H) 484.1, found 484.2.

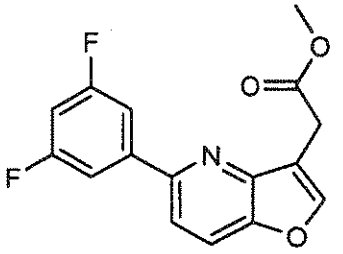
General Method J



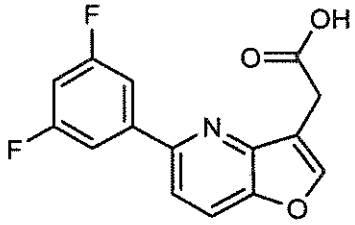


Example 466

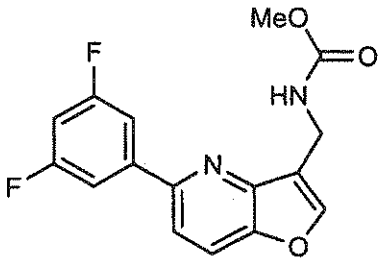
N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine.



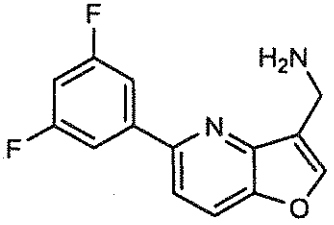
1) methyl 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetate. A sealable microwave vial was charged with methyl 2-(5-chlorofuro[3,2-b]pyridin-3-yl)acetate (1.30 g, 5.74 mmol), palladium(II) acetate (0.129 g, 0.574 mmol), potassium phosphate (3.66 g, 17.2 mmol), 3,5-difluorophenylboronic acid (1.81 g, 11.5 mmol), and X-Phos (0.548 g, 1.15 mmol). The vial was sealed, flushed with N_2, then dioxane (20 mL) and H_2O (2 mL) were added. The solution was sparged with N_2 for 10 min, then heated at 100 °C for 24 h. The mixture was then cooled to rt and concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (120 g) using 98:2 Hexanes : EtOAc to 70:30 Hexanes : EtOAc gradient to afford methyl 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetate (1.46 g, 83.8% yield) as a colorless amorphous solid. LRMS (ESI) *m/z* calcd for $C_{16}H_{12}F_2NO_3$ (M+H) 304.1, found 304.2.



2) 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetic acid. To a flask charged with methyl 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetate (1.46g, 5 mmol) was added MeOH (1.5 mL), H_2O (0.5 mL), followed by NaOH (2 mL, 6 M, 12 mmol) to generate a yellow solution, which was capped and maintained at rt for 18 h. The solution was acidified with conc. HCl to pH=3 and poured into CH_2Cl_2. The layers were separated and the organic layer was extracted with CH_2Cl_2 (2x10 mL), followed by EtOAc (2x10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to produce a colorless solid, which was of sufficient purity for use in the next step.



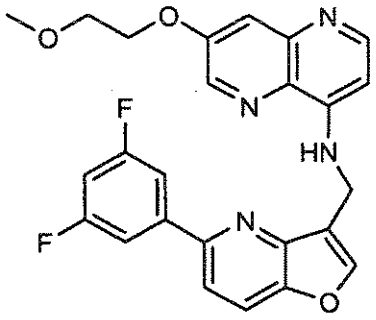
3) methyl (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methylcarbamate. To a flask under N_2 charged with 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetic acid (1.033 g, 3.57 mmol) was added anhydrous CH_2Cl_2 (40 mL). The heterogeneous solution was cooled to 0 °C and oxalyl chloride (1.6 mL, 17.8 mmol) was added, followed by a catalytic amount of DMF. The solution was warmed to rt and maintained for 1 h. The solution was concentrated, then taken up in anhydrous acetone and added to a stirring aqueous solution of sodium azide (1.62 g, 25.0 mmol, in 10 mL H_2O) at 0 °C to generate a homogeneous orange solution. After 15 min at 0 °C, the mixture was diluted further with CH_2Cl_2 and stirred an additional 5 min to give a homogeneous solution. The solution was then partitioned between H_2O and CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was transferred to a dry flask, evacuated and flushed with N_2 (5x), and anhydrous CH_2Cl_2 (30 mL) was added. The solution was cooled to -78 °C, and boron trichloride (5.4 mL, 5.4 mmol, 1.0 M in CH_2Cl_2) was added dropwise. The cold bath was removed and the solution was allowed to warm to rt, and maintained 48 h. Anhydrous methanol (5 mL) was added and the solution maintained at rt for 3 h at which time it was concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (80 g) using 99:1 CH_2Cl_2 : MeOH to 90:10:1 CH_2Cl_2 : MeOH : NH_4OH to afford methyl (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methylcarbamate (680 mg, 60% yield) as a brown amorphous solid. LRMS (ESI) *m/z* calcd for $C_{16}H_{13}F_2N_2O_3$ (M+H) 319.1, found 319.2.



4) (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine. To a flask charged with methyl (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methylcarbamate (680 mg, 2137 μmol)

was added MeOH (20 mL), then aqueous NaOH (18 mL, 6 N, 106 mmol). The solution was heated at reflux for 60 h. The solution was concentrated to remove MeOH, then partitioned between CH_2Cl_2 (30 mL) and $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1x10 mL), then EtOAc (4x25 mL). The combined organic layers were concentrated to give a total of (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine (306.6 mg, 55% yield) as a brown foam. LRMS (ESI) *m/z* calcd for $C_{14}H_{11}F_2N_2O$ (M+H) 261.1, found 261.2.

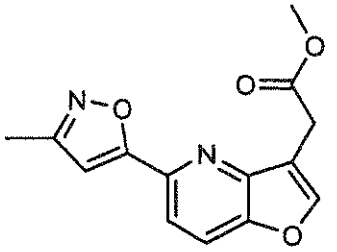
5) N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine. A sealable microwave vial was charged with (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine (177.6 mg, 682 μmol), 8-chloro-3-methoxy-1,5-naphthyridine (146 mg, 751 μmol), and potassium phosphate (435 mg, 2047 μmol). A septum was attached and the vial was flushed with N_2, then toluene (5 mL) and H2O (1 mL) were added and the was solution sparged with N_2 for 5 min. The septum was then quickly removed and tris(dibenzylideneacetone)dipalladium (0) (15.6 mg, 17.1 μmol) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (42.5 mg, 68.2 μmol) were added together as solids. The vial was then sealed and the resulting purple solution was sparged again for 5 min. The mixture was then heated at 100 °C for 20 h. The mixture was concentrated *in vacuo* for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (80 g) using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to afford a tan amorphous solid. This solid was additionally triturated with CH_2Cl_2 (2x0.5 mL) to give N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine (103 mg, 36.1% yield). LRMS (ESI) *m/z* calcd for $C_{23}H_{17}F_2N_4O_2$ (M+H) 419.1, found 419.2.



Example 467

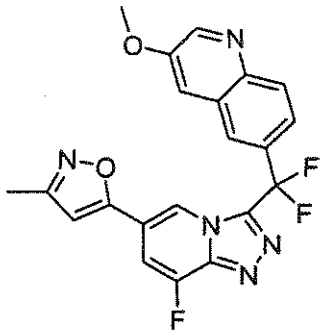
N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-(2-methoxyethoxy)-1,5-naphthyridin-4-amine.

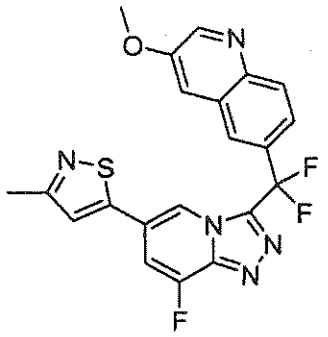
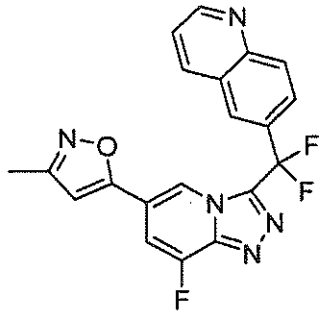
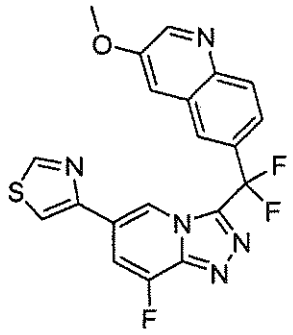
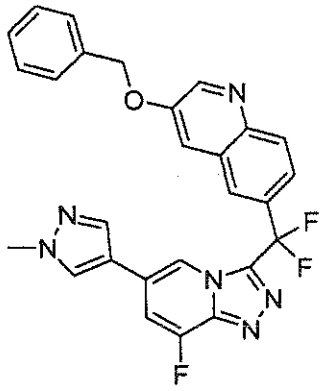
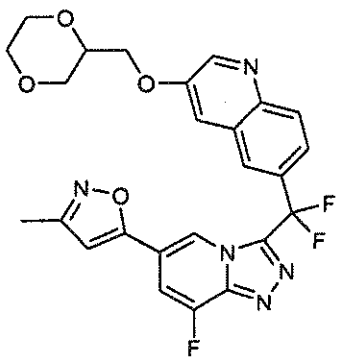
The title compound was assembled from (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine and 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine in the manner described for 7-methoxy-N-((5-(3-methylisoxazol-5-yl)furo[3,2-b]pyridin-3-yl)methyl)-1,5-naphthyridin-4-amine. LRMS (ESI) *m/z* calcd for $C_{25}H_{21}F_2N_4O_3$ (M+H) 463.2, found 463.2.

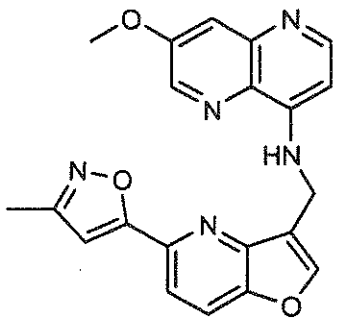


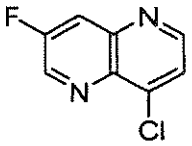
Methyl 2-(5-(3-methylisoxazol-5-yl)furo[3,2-b]pyridin-3-yl)acetate.

A sealable flask was charged with methyl 2-(5-chlorofuro[3,2-b]pyridin-3-yl)acetate, palladium (II) acetate (49.8 mg, 222 μmol), X-Phos (211 mg, 443 μmol), and 3-methyl-5-(tributylstannyl)isoxazole (1319 mg, 3546 μmol). The flask was sealed and dioxane (20 mL) was added. The mixture was sparged with N_2 for 10 min, then heated at 100 °C for 48 h. The mixture was cooled to rt and concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (40 g) using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH to afford methyl 2-(5-(3-methylisoxazol-5-yl)furo[3,2-b]pyridin-3-yl)acetate (581 mg, 96.3% yield). LRMS (ESI) *m/z* calcd for $C_{14}H_{13}N_2O_4$ (M+H) 273.1, found 273.3.

Ex	Structure	MW (M+H)	Mass Found	Method
468		426	426	I

469		442	442	I
470		396	396	I
471		428	428	I
472		501	501	I
473		512	512	I

474		388	388	J



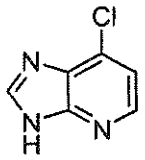
8-chloro-3-fluoro-1,5-naphthyridine

1) 5-((5-fluoropyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione. A 150 mL sealed tube was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (6.0 g, 41.6 mmol) and trimethyl orthoformate (41.6 mL, 41.6 mmol). This was heated to 100 °C, and stirred at this temperature for 2 hours. Reaction then cooled to 30^{0}C and 5-fluoropyridin-3-amine (4.7 g, 41.6 mmol) added portion-wise. Reaction vessel resealed and mixture stirred at 100 °C for 3 hours. LC/MS shows completion. Reaction mixture was cooled to room temperature, diluted with hexane, filtered, and air dried to yield 5-((5-fluoropyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (9.1 g, 82% yield) as a bright yellow solid. MS [M+H]= 267.2. Calc'd for $C_{12}H_{11}FN_2O_4$=266.2.

2) 7-fluoro-1,5-naphthyridin-4(1H)-one. A 500 mL round bottom flask equipped with a reflux condenser was charged with 5-((5-fluoropyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (8.0 g, 30.0 mmol) and diphenyl ether (83.5 mL). This was heated to 250 °C in heating mantle and allowed to stay at this temperature for five minutes. Cooled to room temperature, diluted with hot hexanes, and filtered to afford 7-fluoro-1,5-naphthyridin-4(1H)-one (2.2 g, 45% yield) as a crude brown solid. The title compound was used without further purification. MS [M+H]=165.2, Calc'd for $C_8H_5FN_2O$=164.14.

3) 8-chloro-3-fluoro-1,5-naphthyridine. A pressure resistant vial was charged with 7-fluoro-1,5-naphthyridin-4(1H)-one (600 mg, 3.66 mmol) and POCl3 (6.8 mL, 73.1 mmol). Vessel sealed and stirred at 110^{0}C for 16hrs. Reaction mixture was cooled to room temperature and poured onto ice while stirring vigorously. While keeping reaction mixture at 0^{0}C, it was basified to pH~8 with 6N NaOH. Product extracted with dichloromethane. Organic layer

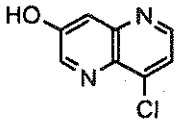
collected, dried over sodium sulfate and concentrated to afford desired material. This was passed through a silica plug in 1-5% (90:10:1 DCM/MeOH/NH_4OH)/DCM to afford 8-chloro-3-fluoro-1,5-naphthyridine (430mg, 64% yield) as a tan solid. MS [M+H]=182.9. Calc'd for $C_8H_4ClFN_2$=182.58



7-chloro-3H-imidazo[4,5-b]pyridine

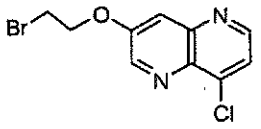
1) 4-azabenzimidazole N-oxide . Hydrogen peroxide (30wt% solution in water, 38.0 ml, 372 mmol) was added to a suspension of 3H-imidazo[4,5-b]pyridine (4.93 g, 41.4 mmol) in AcOH (40 mL) at room temperature. The reasulting reaction mixture was stirred at 80°C for 3h, cooled to RT and concentrated in vacuo to a volume ~50 mL. Concentration to dryness was done using a stream of N_2. The resulting residue was suspended in water (~10mL). Filtration afforded the title compound (4.61g, 82.4% yield).

2) 7-chloro-3H-imidazo[4,5-b]pyridine. A 50mL round bottom flask set up with a reflux condenser under nitrogen atmosphere was charged 4-azabenzimidazole N-oxide (1.2 g, 8.88 mmol) and 11 mL of DMF. This was heated to 50°C and methanesulfonyl chloride (1.86 ml, 23.98 mmol) was added dropwise via syringe. The resulting mixture was heated to 80°C and stirred at this temperature for 16 hours. This was cooled to room temperature and quenched with water (approximately 10 mL) and reaction mixture brought to pH 7 by adding 6N NaOH aqueous solution. The reaction was extracted four times with dichloromethane (50mL). Some product was present in aqueous layer; this was concentrated and residue set aside. The combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (RediSep 40g column, gradient elution 0-10% MeOH:DCM) to afford 7-chloro-3H-imidazo[4,5-b]pyridine (450mg, 33.0% yield). MS [M+H]=154.2. Calc'd $C_6H_4ClN_3$ = 153.56.



8-chloro-1,5-naphthyridin-3-ol

A pressure-resistant vial was charged with 8-chloro-3-methoxy-1,5-naphthyridine (2.5 g, 12.8 mmol), boron tribromide (13.4 mL, 141.3 mmol) and dichloroethane (0.6M, 21.4mL). Vessel sealed and mixture stirred at 60^{0}C for 16hrs. Next day the reaction mixture was chilled in ice bath and diluted with dichloromethane (200mL). This was allowed to sit under nitrogen system until all fuming ceased. The resulting yellow solid material was then filtered and dried under high vacuum. This was suspended in 40% (90:10:1 DCM/MeOH/NH4OH)/DCM and purified in this system by ISCO silica gel chromatography (80g) afford 8-chloro-1,5-naphthyridin-3-ol (1.3g, 56% yield). MS [M+H]=181.2. Calc'd for $C_8H_5ClN_2O$=180.59.

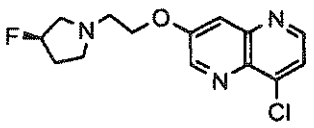


3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine.

A resealable pressure bottle was charged with 8-chloro-1,5-naphthyridin-3-ol (400mg, 2.2 mmol), 2-dibromoethane (3.2 mL, 37.7 mmol), and DMF (0.15M, 14.8 mL). Vessel sealed and placed in a pre-heated at 65^{0}C oil bath. Reaction allowed to stir at this temperature for 4hrs. Reaction cooled to room temperature and passed through a pad of celite. Filtrate concentrated and purified by ISCO silica gel chromatography (20-40%EtOAc/Hexanes) to afford 3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine (460mg, 72% yield). MS [M+H]=289.0 Calc'd for $C_{10}H_8BrClN_2O$=287.54

The following compound was prepared using the procedure for 3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine:

8-chloro-3-((tetrahydrofuran-2-yl)methoxy)-1,5-naphthyridine;
8-chloro-3-((tetrahydrothiophen-1,1-dioxide-3-yl)methoxy)-1,5-naphthyridine (starting with the alkyl chloride).



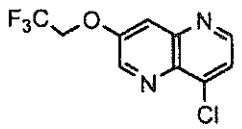
(R)-8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine.

A 25mL round bottom flask at rt was charged with (R)-3-fluoropyrrolidine hydrochloride (124 mg, 0.99 mmol). To this was added potassium carbonate (365 mg, 2.64 mmol), 3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine (190mg, 0.66 mmol), sodium iodide (149 mg, 0.99

mmol) and DMF (2mL). Reaction mixture placed in oil bath preheated to 60^{0}C and allowed to stir for 16hrs. Reaction mixture passed through celite cake, rinsed with 10%MeOH/DCM and filtrate concentrated to afford yellow oil. This was purified by ISCO silica gel chromatography (20-40% EtOAC/Hexanes) to afford (R)-8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine (105mg, 54% yield). MS [M+H]=296.2. Calc'd for $C_{14}H_{15}ClFN_3O$=295.7.

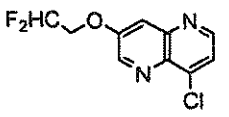
The following compounds were prepared in a similar fashion as 8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine:

8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine;
8-chloro-3-(2-(3,3-difluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine;
1-(2-(8-chloro-1,5-naphthyridin-3-yloxy)ethyl)pyrrolidin-3-ol;
3-(2-(1H-1,2,4-triazol-1-yl)ethoxy)-8-chloro-1,5-naphthyridine (using NaH as the base);
3-(2-(1H-pyrazol-1-yl)ethoxy)-8-chloro-1,5-naphthyridine;
3-(2-(1H-1,2,3-triazol-1-yl)ethoxy)-8-chloro-1,5-naphthyridine.



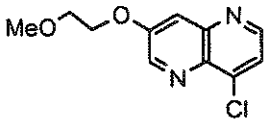
8-chloro-3-(2,2,2-trifluoroethoxy)-1,5-naphthyridine.

A resealable pressure bottle was charged with 8-chloro-1,5-naphthyridin-3-ol (80mg, 0.44 mmol), cesium carbonate (433 mg, 1.3 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (360 mg, 1.55 mmol), and DMF (0.9 ml). Vessel sealed and placed in a pre-heated at 50^{0}C oil bath. Reaction allowed tostir at this temperature for 45 minutes. LC/MS shows complete conversion. Quench with water, dilute with aqueous sodium bicarbonate solution and dichloromethane. Layers separated, organic layer collected and dried over sodium sulfate. This was concentrated to afford yellow oil; which was purified by ISCO silica gel chromatography (20-40%EtOAc/Hexanes) to afford 8-chloro-3-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (65mg, 56% yield). MS [M+H]=263.0@1.89minutes. Calc'd for $C_{10}H_6ClF_3N_2O$=262.6.



8-chloro-3-(2,2-difluoroethoxy)-1,5-naphthyridine.

The title compound was prepared using the method described for 8-chloro-3-(2,2,2-trifluoroethoxy)-1,5-naphthyridine.

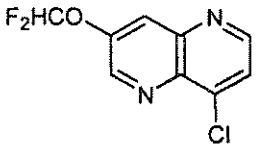


8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine.

A round bottom flask under nitrogen environment was charged with 8-chloro-1,5-naphthyridin-3-ol (1.05 g, 5.8 mmol), 22.8 g of PS-Triphenylphosphine (loading: 2.2mmol/g), 2-methoxyethanol (2.2 mL, 27.9 mmol), and THF (29.1 ml, 5814 μmol)/ DCM (58.1 mL). Mixture cooled to 0^0C and to this was added DEAD (1.84 mL) dropwise via syringe. Reaction mixture allowed to stir at room temperature for 16 hours. Diluted with 50mL of 10%MeOH/dichloromethane and resin bound reagent filtered. Filtrate concentrated under reduced pressure and purified by ISCO silica gel chromatography (10-30% EtOAc/Hexanes) to afford 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine (770mg, 55% yield) as white solid. MS [M+H]=238.9. Calc'd for $C_{11}H_{11}ClN_2O_2$=238.67.

The following compounds were prepared in a similar fashion as 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine:

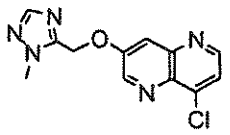
8-chloro-3-(2-(pyrrolidin-1-yl)ethoxy)-1,5-naphthyridine;
8-chloro-3-(3-morpholinopropoxy)-1,5-naphthyridine;
3-((1,4-dioxan-2-yl)methoxy)-8-chloro-1,5-naphthyridine;
8-chloro-3-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridine.



8-chloro-3-(difluoromethoxy)-1,5-naphthyridine.

A round bottom flask under nitrogen atmosphere was charged with sodium 2-chloro-2,2-difluoroacetate (0.49 g, 3.2 mmol), 8-chloro-1,5-naphthyridin-3-ol (0.25 g, 1.4 mmol), cesium carbonate (1.4 g, 4.2 mmol), and DMF (2.8 mL, 0.5M). This was then placed in a 100^0C preheated oil bath and stirred at this temperature for 3 hours. Reaction mixture diluted with 10%Methanol/Dichloromethane and filtered over celite. Filtrate concentrated and purified by ISCO silica gel chromatography (40g) in 1%MeOH/DCM to afford pure 8-chloro-3-

(difluoromethoxy)-1,5-naphthyridine (0.18 g, 56% yield) as white solid. MS [M+H]=231.2. Calc'd for $C_9H_5ClF_2N_2O$=230.60.

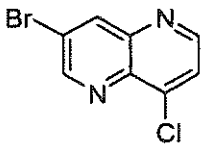


8-chloro-3-((2-methyl-2H-1,2,4-triazol-3-yl)methoxy)-1,5-naphthyridine

1) 2-methyl-2H-1,2,4-triazole-3-carbaldehyde. A dry round bottom flask under nitrogen atmosphere was charged with 1-methyl-1H-1,2,4-triazole (1.0 g, 12.04 mmol) and THF (6.0 ml, 2M). This was cooled to 0^0C followed by addition of 2M solution of isopropylmagnesium chloride in THF (6.6 mL, 13.24 mmol) via syringe. Ice bath removed and reaction allowed to stir at room temperature for 1.5 hours. Reaction mixture cooled back to 0^0C and N,N-dimethylformamide (1.39 ml, 18.05 mmol) added dropwise via syringe. Reaction mixture allowed to warm up to room temperature over 1 hour and stirred at this temperature for 16 hours. Next day reaction mixture was quenched with 2N HCl and mixture diluted with dichloromethane. Layers separated, and aqueous layer neutralized with aq. sodium bicarbonate solution and extracted with dichloromethane. All organic layers combined, dried over sodium sulfate and concentrated at room temperature (most THF remains) to afford clear material. This was purified by ISCO silica gel chromatography (10-40%EtOAc/Hex) to afford 2-methyl-2H-1,2,4-triazole-3-carbaldehyde (1.0 g, 75% yield). Yield was estimated based on H'NMR. Product was isolated as a solution in EtOAc (did not remove all EtOAc due to volatility of aldehyde, b.p.~60^0C). MS [M+H] = 112.2; MS [M+H+H_2O] = 130.2@0.23minutes . Calc'd for $C_4H_5N_3O$ = 111.10.

2) (2-methyl-2H-1,2,4-triazol-3-yl)methanol. 2-methyl-2H-1,2,4-triazole-3-carbaldehyde (0.50 g, 4.50 mmol) in MeOH (10 mL)was treated with sodium borohydride (0.17 g, 4.50 mmol) at room temperature and allowed to stir for 2 hours. Reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with 10%MeOH/DCM, and organic layer collected. Aqueous layer was saturated with sodium sulfate and extracted with 50 mL of dichloromethane (3 times). Organic portions combined, dried over sodium sulfate and concentrated to 1/4 volume at room temp. This was then diluted with ether, causing a precipitate to form. This was concentrated yielding 2-methyl-2H-1,2,4-triazol-3-yl)methanol as a foamy white solid (0.44 g, 86.4% yield). This was used 'as is' for next step. MS [M+H]= 114.2. Calc'd for $C_4H_7N_3O$=113.1.

3) 8-chloro-3-((2-methyl-2H-1,2,4-triazol-3-yl)methoxy)-1,5-naphthyridine. The title compound was prepared in a similar fashion as 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine.



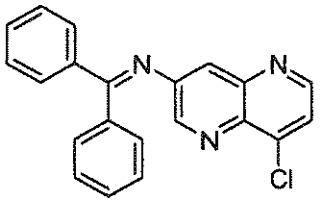
3-bromo-8-chloro-1,5-naphthyridine

1) 5-((5-bromopyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione. A 350mL sealed tube was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (21.6 g, 150.0 mmol) and triethyl orthoformate (150 mL, 150.0 mmol). This was heated to 100 °C, and stirred at this temperature for 2 hours. Reaction then cooled to 30^{0}C and 55-bromopyridin-3-amine (25.95 g, 150.0 mmol) added portion-wise. Reaction vessel resealed and mixture stirred at 100 °C for 3 hours. LC/MS shows completion. Reaction mixture was cooled to room temperature, diluted with hexane, filtered, and air dried to yield 5-((5-bromopyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (41.5 g, 85% yield) as a yellow solid. MS [M+H]= 327.0. Calc'd for $C_{12}H_{11}BrN_2O_4$=327.1.

2) 7-bromo-1,5-naphthyridin-4(1H)-one. A 500 mL round bottom flask equipped with a reflux condenser was charged with 5-((5-bromopyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (10.5 g, 32.1 mmol) and diphenyl ether (84.5 mL, 32.1 mmol). This was heated to 250 °C in heating mantle and allowed to stay at this temperature for 1 hour. Reaction mixture was cooled to room temperature and diluted with 300mL of Hexanes. This was heated to 60^{0}C and triturated in this system for 3 hrs to afford 7-bromo-1,5-naphthyridin-4(1H)-one (6.05 g, 84% yield) as a crude brown solid. This was used without further purification. MS[M+H]=227.0. Calc'd for $C_8H_5BrN_2O$=225.0.

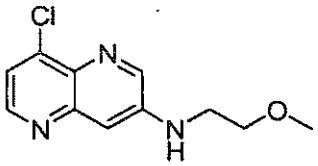
3) 3-bromo-8-chloro-1,5-naphthyridine. 7-bromo-1,5-naphthyridin-4(1H)-one (23.8 g, 105.8 mmol), acetonitriel (192 mL, 105.8 mmol), and DMF (2.05 mL, 26.5 mmol) were placed in a 3-necked round bottom flask set up with a reflux condenser. Argon bubbled through. Reaction mixture brought to reflux (~95^{0}C). Oxalyl chloride (28.7 ml, 328.1mmol) was added dropwise via addition funnel over 40 minutes and reaction allowed to stir at this temperature for 16 hrs. Reaction mixture cooled to 0^{0}C and basified to pH ~8 with aqueous sodium bicarbonate solution. Product extracted with DCM (500mL) three times. Organic layers combined, dried

over sodium sulfate and concentrated to afford brown solid. This was purified by ISCO silica gel chromatography to afford 3-bromo-8-chloro-1,5-naphthyridine (3.6 g, 14% yield) as fluffy tan solid. MS[M+H]=245.0@. Calc'd for $C_8H_4BrClN_2$=243.5.

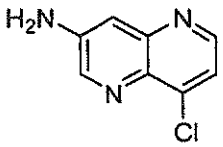


8-chloro-N-(diphenylmethylene)-1,5-naphthyridin-3-amine

A 25ml round bottom flask set up under nitrogen was charged with $Pd_2(dba)_3$ (301mg, 0.33mmol), BINAP (614 mg, 0.99 mmol) and sodium tert-butoxide (237mg, 2.46 mmol). System was purged with Argon and 3-bromo-8-chloro-1,5-naphthyridine (400mg, 1.64 mmol), diphenylmethanimine (0.28 mL, 1.64 mmol), and toluene (1M, 1.64 mL) were added. This was placed in a preheated oil bath at 80^{0}C and stirred at this temperature for 16 hours. Reaction cooled to room temperature, diluted with dichloromethane, and passed over a celite cake. Filtrate collected was concentrated to afford brown oil. This was purifed by ISCO silica gel chromatography (40g, 1%MeOH/DCM over 50mins) to afford clean 8-chloro-N-(diphenylmethylene)-1,5-naphthyridin-3-amine (280mg, 50% yield). MS[M+H]=344.0. Calc'd for $C_{21}H_{14}ClN_3$ =343.8.

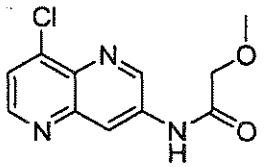


8-chloro-N-(2-methoxyethyl)-1,5-naphthyridin-3-amine.



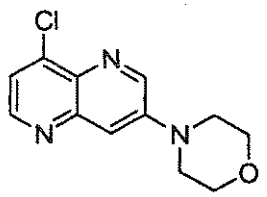
1) 8-chloro-1,5-naphthyridin-3-amine. A round bottom flask under nitrogen was charged with 8-chloro-N-(diphenylmethylene)-1,5-naphthyridin-3-amine (315mg, 0.92 mmol), 2M aqueous HCl (1.42 mL, 2.84 mmol), and tetrahydrofuran (0.25M, 3.67mL). This was stirred at RT for 30 minutes. Reaction basified with aq. sodium bicarbonate solution and product extracted with dichloromethane. This was dried over sodium sulfate and concentrated to afford orange solid; which was purified via ISCO silica gel chromatography, 40g column, 30% (90/10/1 DCM:MeOH:NH4OH)/DCM over 40 minutes to afford 7-amino-1,5-naphthyridin-4-ol (140mg, 95% yield) as yellow solid. MS[M+H]=180.2. Calc'd for $C_8H_6ClN_3$=179.6.

2) 8-chloro-N-(2-methoxyethyl)-1,5-naphthyridin-3-amine. A round bottom flask under nitrogen atmosphere was charged with 8-chloro-1,5-naphthyridin-3-amine (160mg, 0.89 mmol), DMF (2.2 mL, 0.89 mmol). This was cooled to 0^0C and SODIUM HYDRIDE (60% dispersion in oil) (107 mg, 4.45 mmol) added portionwise. This was quickly followed by addition of 1-bromo-2-methoxyethane (0.12 mL, 1.25 mmol) dropwise via syringe. Ice bath removed and reaction mixture heated to 85^0C and stirred at this temperature for 16 hours. Reaction diluted with 5mL of 5%MeOH/Dichloromethane, loaded onto silica gel column and eluted with 2%MeOH/DCM to afford 8-chloro-N-(2-methoxyethyl)-1,5-naphthyridin-3-amine (70mg, 33% yield) as a light yellow solid. MS[M+H]=238.2. Calc'd for $C_{11}H_{12}ClN_3O$=237.7.



N-(8-chloro-1,5-naphthyridin-3-yl)-2-methoxyacetamide

A round bottom flask under nitrogen was charged with 8-chloro-1,5-naphthyridin-3-amine (41mg, 0.23 mmol), triethylamine (64 µl, 0.46 mmol), and dichloromethane (1mL). To this was added 2-methoxyacetyl chloride (42 µl, 0.46 mmol) dropwise via syringe and reaction allowed to stir overnight at room temperature. Next day reaction mixture was diluted with dichloromethane and washed with aqueous sodium bicarbonate solution. Layers separated and organic layer dried over sodium sulfate to afford yellow oil. This was purified by ISCO silica gel chromatography (2-5%MeOH/DCM) to afford N-(8-chloro-1,5-naphthyridin-3-yl)-2-methoxyacetamide (43mg, 75% yield) as light yellow solid. MS[M+H]=251.9. Calc'd for $C_{11}H_{10}ClN_3O_2$=251.7.



8-chloro-3-morpholino-1,5-naphthyridine

A round bottom flask under nitrogen atmosphere was charged with $Pd_2(dba)_3$ (578 mg, 0.63 mmol), Xantphos (1.1 g, 1.89 mmol) , and sodium tert-butoxide (364 mg, 3.79 mmol). This was purged with Argon followed by addition of 3-bromo-8-chloro-1,5-naphthyridine (615 mg, 2.53 mmol), morpholine (0.22 mL, 2.53 mmol), and toluene (1M, 2.53 mL). This was then placed in a preheated oil bath at 80^0C. After 2.5 hours, reaction was stopped, cooled to room

temp and diluted with Dichloromethane. This was passed over a celite cake and filtrate concentrated to afford brown oil; which was purifed by ISCO silica gel chromatography (40g, 1%MeOH/DCM over 50mins) to afford 8-chloro-3-morpholino-1,5-naphthyridine (200mg, 32% yield). MS[M+H]=250.2. Calc'd for $C_{12}H_{12}ClN_3O$=249.7.

4-bromo-1-phenyl-1H-pyrazole.

A sealable tube was charged with 4-bromopyrazole (4.000 g, 27.2 mmol), 1-iodobenzene (3.64 ml, 32.7 mmol), (+/-)-trans-1,2-diaminocyclohexane (0.654 ml, 5.44 mmol), Copper iodide (I) (0.518 g, 2.72 mmol), potassium carbonate (8.28 g, 59.9 mmol) and 13 mL dioxane added. The mixture was blanketed with N2, the vessel sealed and heated to 100 C for 16 h. The mixture was allowed to cool to rt, diluted with EtOAc, washed with water, and an emullsion formed. The organic layer separated and the aqueous emulsion mixture was filter through a pad of celite and rinsed with EtOAc, and sat. $NaHCO_3$. The combined organig layers were dried over Na_2SO_4, filtered and evaporate. The mixture was purified via flash chromatography using a 0 % to 100 % CH_2Cl_2 in hexanes gradient. The title compound was collected as a yellow solid (3.18 g)

1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-phenyl-1H-pyrazole.

4-bromo-1-(tetrahydrofuran-3-yl)-1H-pyrazole

The title compound was prepared in the same manner as 4-bromo-1-(cyclobutyl)-1H-pyrazole, but using tetrahydrofuran-3-yl methanesulfonate (prepared according to procedures known in the art).

1-(tetrahydrofuran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-(tetrahydrofuran-3-yl)-1H-pyrazole.

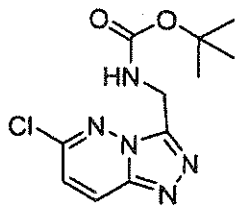
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1-cyclopropyl-1H-pyrazole

a) 1-cyclopropyl-1H-pyrazole . In a 1000 mL 3-neck flask, to a mixture of potassium hydroxide (104 g, 1857 mmol) in water (200 mL) was added cyclopropylamine (131 ml, 1857

mmol) and the mixture stirred at 50 C. A solution of hydroxylamine-O-sulfonic acid (HOS)(30.00 g, 265 mmol) in 100 mL water was added dropwise resulting in the formation of a white precipitate after the first few drops. The stirring stopped during the first half of the addition and some cyclopropylamine condensed on top of the HOS soln. Additional amine (10 mL) was added to the reaction and addition of HOS solution continuted. Mixture bubbles during the addition. The flask was remove from heat and cool in ice bath to 25 C. HCl (conc) was added slowly, 150-200 mL, to achieve PH 3. The mixture was filtered to remove the white solid and the filtrate heated with 1,1,3,3-tetramethoxypropane (43.7 ml, 265 mmol). The mixture took 1.5 h to reach 90 C, maintained the temperature at 90 for 1 h, then allowed the mixture to cool to 40 C with stirring for an additional 17 h. The mixture was allowed to cool to ~35 C and extracted with Et_2O (400 mL then 2 x100 mL), the combined organic layers were with water, 6N NaOH, 2N NaOH, then sat NaHCO3, and the organic layer dried over Na_2SO_4, filtered and evaporate gently. Upon evaporation, when volume is reduced from ~600 mL to ~100 mL, the white solid that has precipitated was filtered. The title compound was obtained as a golden liquid (~ 2g).

b) 4-bromo-1-cyclopropyl-1H-pyrazole. To a golden solution of 1-cyclopropyl-1H-pyrazole (2.360 g, 22 mmol) in 100 mL chloroform, was added bromine (1.2 ml, 24 mmol) as a soln in 100 mL $CHCl_3$ dropwise over 1.5 h. the mixture was heated in oil bath to 60 C for 2 h. The mixture was allowed to cool to RT, washed with sat $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to afford the title compound as a tan liquid (3.64 g).

c) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1-cyclopropyl-1H-pyrazole. The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-cyclopropyl-1H-pyrazole.

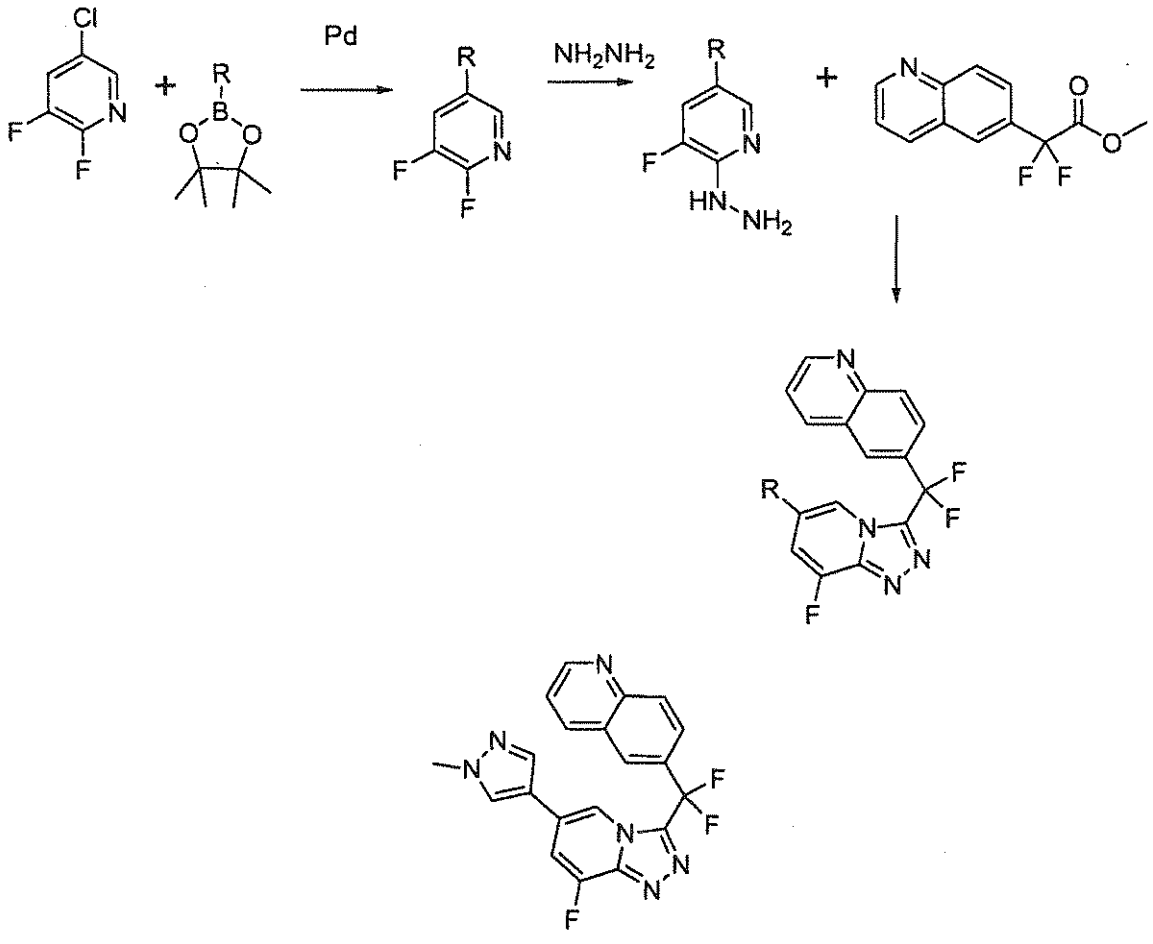


tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate .

A 2-L round bottom flask flask equipped with a magnetic stirbar was charged with di(1H-imidazol-1-yl)methanone (121 g, 749 mmol) and acetonitrile (500 mL). The stirred slurry was cooled by immersing the flask in an ice bath. A solution of N-Boc glycine (125 g, 714 mmol)

in acetonitrile (500 mL) was added via a 500-mL addition funnel over the course of 30-45 min. The mixture was aged for 1 h while a 5-L, 3-neck, round bottom flask equipped with a mechanical overhead stirrer and a thermocouple w/adapter was charged with 1-(6-chloropyridazin-3-yl)hydrazine (108 g, 749 mmol) and acetonitrile (900 mL) and cooled to <5 deg C in an ice bath. The cold solution of the acylimidazole was then transferred via a polyethylene cannula into the thick suspension of the hydrazine over a period of 30-45 min). The ice bath was removed, and the mixture was allowed to warm. After 2.5 h of stirring, 4-methylbenzenesulfonic acid hydrate (143 g, 749 mmol) was added. The flask was then equipped with a heating mantle and a reflux condenser and was heated to reflux (82 deg C) for 13 h, then cooled back to about 60 deg C. At this point, the warm solution was vacuum filtered through paper. The brown filtrate was then concentrated by rotary evaporation. The resulting thick yellow-brown slurry was stirred in an ice bath and diluted with ACN (about 100 mL). After stirring for 1 h, the solids were isolated by vacuum filtration, washed with ice-cold 1:1 ACN/H_2O (2x150 mL) and air-dried on the filter until a freely flowing solid was obtained (159 g, 78.5% yield).

General Method K

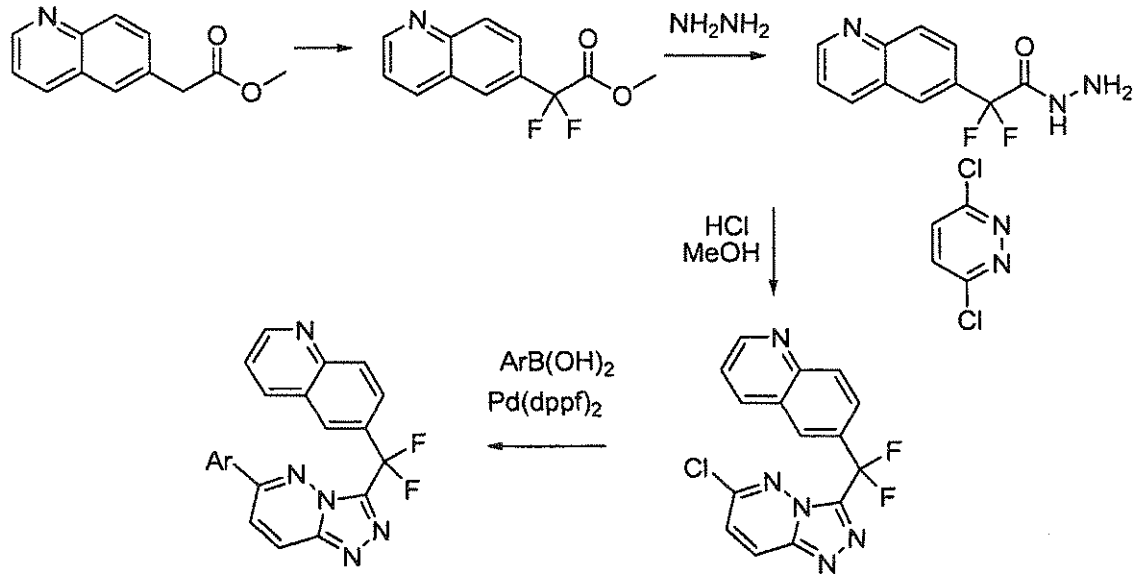


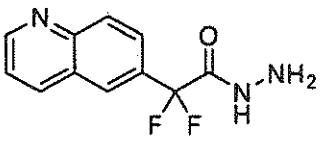
Example 475

6-(Difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline.

To a stirring suspension of 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (190 mg, 917 μmol), methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (218 mg, 917 μmol), triphenylphosphine polymer supported (241 mg, 917 μmol), DIEA (200 μl, 1146 μmol) in DCM (4mL) was added 2,2,2-trichloroacetonitrile (92 μl, 917 μmol). The reaction vessel was then appropriately sealed and heated to 150 °C with microwaves for 15 min. The reaction was then concentrated onto dry silica under reduced pressure and product purified on silica (40 g) eluting with 1-4% of 2 M NH_3 in MeOH/DCM. The product was then further purified by RP-HPLC eluting with water/ACN (0.1% TFA). Collected fractions concentrated under reduced pressure, dissolved in MeOH/DCM (5mL) and stirred with Si-Carbonated (300 mg; 0.2 mmol) for 30 min at 23 °C. Solids were then removed by filtration, and washed with MeOH (3x1mL). The filtrate was then concentrated under reduced pressure, and product isolated as an off white solid. MS (ESI pos. ion) m/z: 395 (MH+). Calc'd exact mass for $C_{20}H_{13}F_3N_6$: 394.

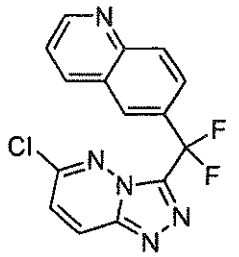
General Method L





2,2-Difluoro-2-(quinolin-6-yl)acetohydrazide

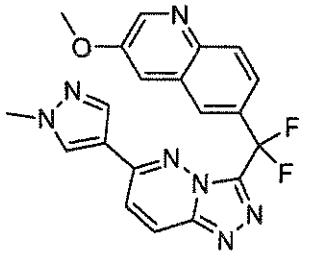
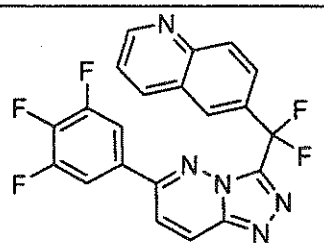
A solution methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (400 mg, 1686 μmol) and anhydrous hydrazine (2153 μl, 67453 μmol) in MeOH (4 mL) was stirred for 1 h at 23 °C. The solvents were then removed under reduced pressure to provide product as a white solid. MS (ESI pos. ion) m/z: 238 (MH+). Calc'd exact mass for $C_{11}H_9F_2N_3O$: 237.

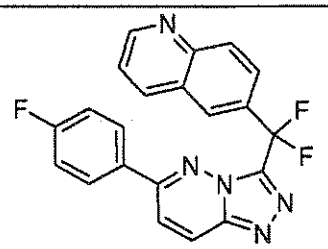
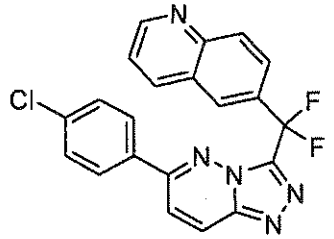
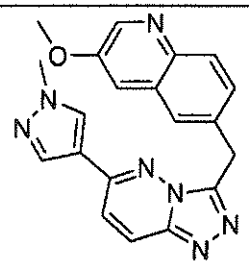
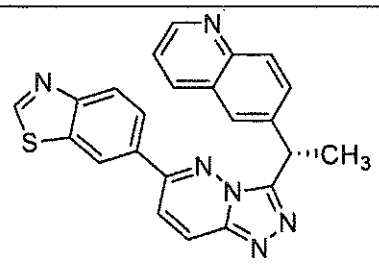
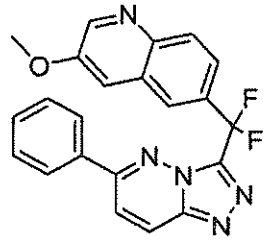


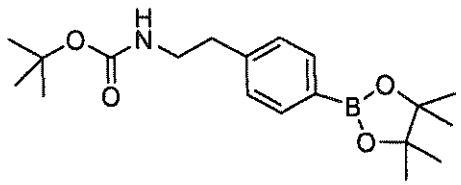
Example 476

6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)quinoline

A suspension of 2,2-difluoro-2-(quinolin-6-yl)acetohydrazide (2000 mg, 8432 μmol) and 3,6-dichloropyridazine (3768 mg, 25295 μmol) in 1.25 M HCl in MeOH (20 mL) was heated to 90 °C with microwaves for 50 min. The solvents were then removed under reduced pressure and residue partitioned between 9:1 $CHCl_3$/IPA (60 mL) and 1 M NaOH (20 mL). The organic phase then dried over $MgSO_4$, concnetrated, then purified on silica (120 g) eluting with 1>2.5% of 2 M NH_3 in MeOH/DCM to provide product isolated as a dark tan soild. MS (ESI pos. ion) m/z: 332 (MH+). Calc'd exact mass for $C_{15}H_8ClF_2N_5$: 331.

Ex	Structure	MW	Mass Found	Method
477		407	408	L
478		427	428	L

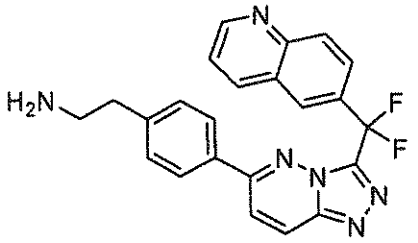
479		391	392	L
480		407	408	L
481		371	372	M
482		408	409	M
483		403	404	M



<u>*tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethylcarbamate</u>

A suspension of tert-butyl 4-bromophenethylcarbamate (2700 mg, 8994 μmol), bis(pinacolato)diboron (2284 mg, 8994 μmol), bis(pinacolato)diboron (2284 mg, 8994 μmol), potassium acetate (1765 mg, 17989 μmol) in dioxane (12mL) was sparged with argon for 5 min then heated to 120 °C in an appropriately sealed vessel for 1 h. The reaction was then

partitioned between ether (50 mL) and 5% $NaHCO_3$ (25 mL). The organic phase was then dried over $MgSO_4$, concentrated, then purified on silica (120 g) eluting with 10>30% EtOAc/Hexanes. The product tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethylcarbamate (2200 mg, 70% yield) was isolated as a white solid. MS (ESI pos. ion) m/z: 292 (MH+1-56). Calc'd exact mass for $C_{19}H_{30}BNO_4$: 347.



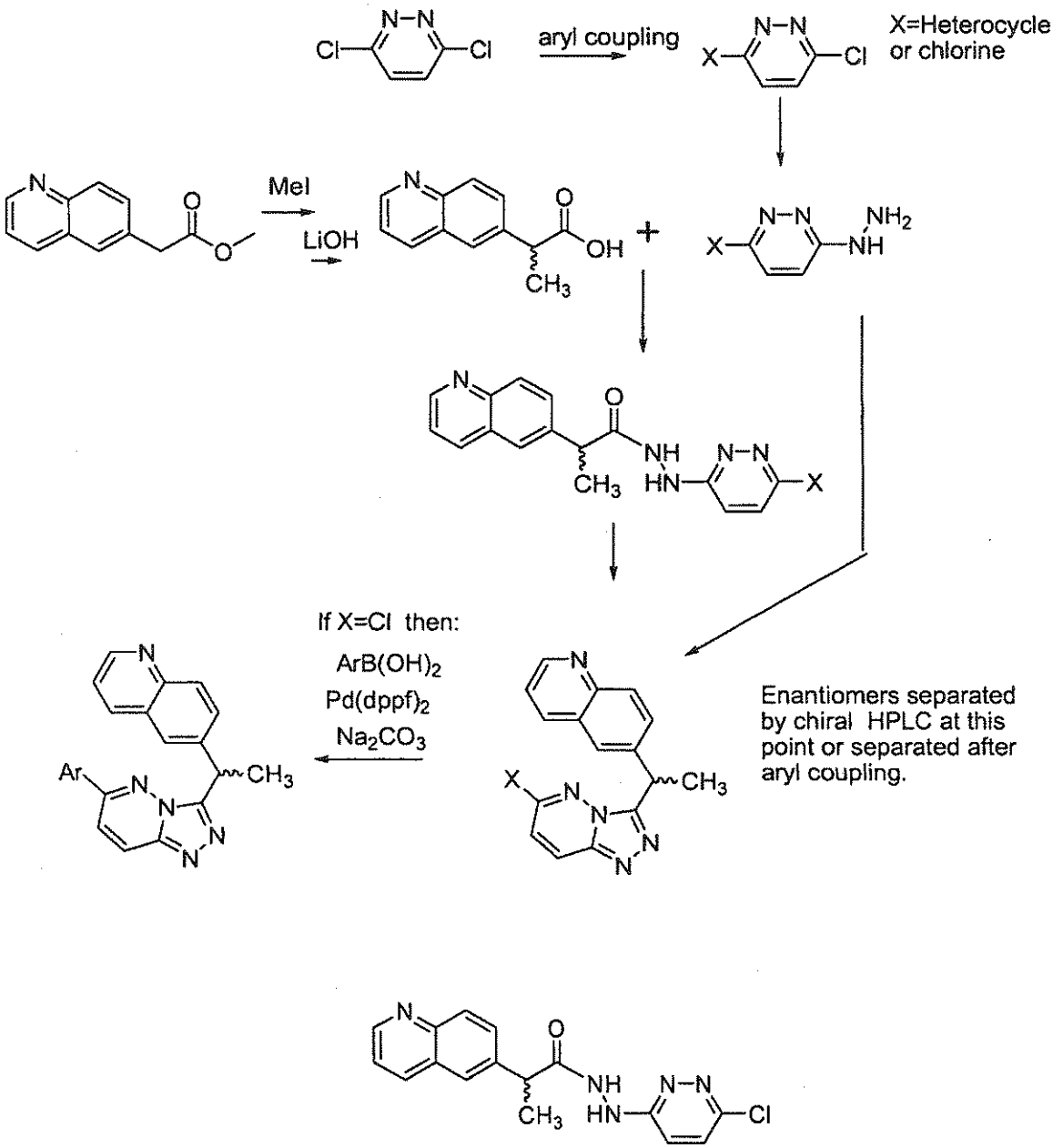
Example 484

2-(4-(3-(Difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethanamine

a) *tert*-Butyl 2-(4-(3-(difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethylcarbamate. A suspension of 6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)quinoline (350 mg, 1055 µmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethylcarbamate (733 mg, 2110 µmol), 1,1'-bis (diphenylphosphino)ferrocene-palladium(ii)dichloride dichloromethane complex (77 mg, 106 µmol), Na2CO3 (447 mg, 4221 µmol) in DME (4mL) and water (2mL) was sparged with argon for 5 min then heated to 85 °C in an appropriately sealed vessel for 4 h. The reaction was then partitioned between DCM (30 mL) and 1 M NaOH (10 mL). The organic phase was then dried over $MgSO_4$, concentrated, then purified on silica (40 g) eluting with 1>4% of 2 M NH_3 in MeOH/DCM. The product was isolated as an off white solid.

b) 2-(4-(3-(Difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethanamine. A solution of tert-butyl 2-(4-(3-(difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethylcarbamate (70 mg, 136 µmol) in DCM (1 mL) and TFA (1 mL) was stirred for 30 min at 23 °C. The solvents were then removed under reduced pressure and crude product purified by RP-HPLC eluting with water/ACN (0.1% TFA). The desired collected fractions were then concentrated under reduced pressure and the resulting residue dissolved in MeOH/DCM (5 mL). Solution was then stirred as a suspension with Si-Carbonated (300 mg; 0.2 mmol) for 30 min at 23 °C. The solids were then removed by filtration, washed with MeOH (3x1mL), and filtrate concentrated under reduced pressure. The product was isolated as a white fluffy solid. MS (ESI pos. ion) m/z: 417 (MH+). Calc'd exact mass for $C_{23}H_{18}F_2N_6$: 416.

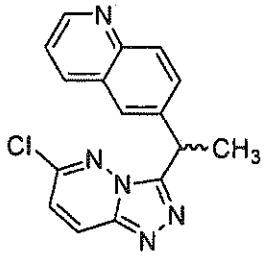
General Method M



N'-(6-chloropyridazin-3-yl)-2-(quinolin-6-yl)propanehydrazide

To a stirring solution of 2-(quinolin-6-yl)propanoic acid (3260 mg, 16201 μmol) and DIEA (2830 μl, 16201 μmol) in DMF (25 mL) was added o-(7-azabenzotriazol-1-yl)-n,n,n',n-tetramethyl uronium hexafluorophosphate (6160 mg, 16201 μmol) whole at 23 °C under nitrogen. The solution was stirred for 60 min, cooled to 0°C, then added 1-(6-chloropyridazin-3-yl)hydrazine (2342 mg, 16201 μmol). After 20 h stirring at 23 °C, the reaction was then partitioned between 9:1 $CHCl_3$/IPA (100 mL) and 5% $NaHCO_3$ (50 mL). The organic phase

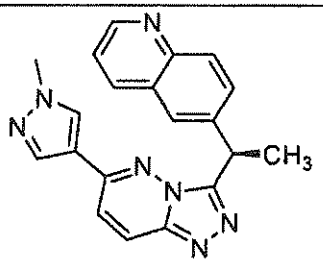
was then dried over $MgSO_4$, concentrated to an oil, then purifed on silica (120 g) eluting with 0>10% of 2 M NH_3 in MeOH/DCM. The product was isolated as an off white solid. MS (ESI pos. ion) m/z: 328 (MH+). Calc'd exact mass for $C_{16}H_{14}ClN_5O$: 327.

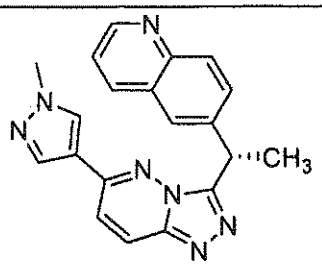
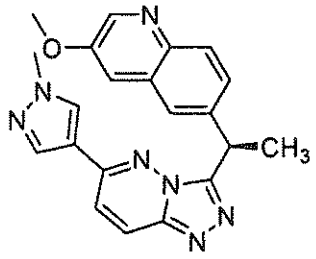
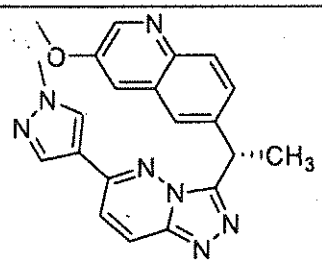
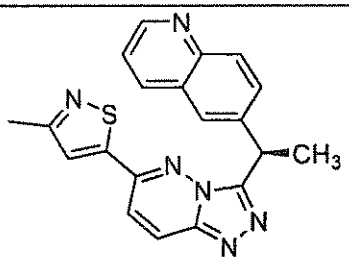
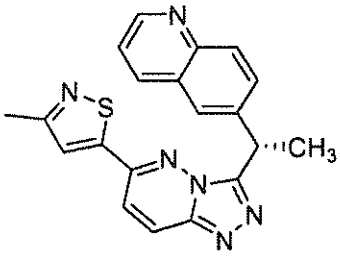


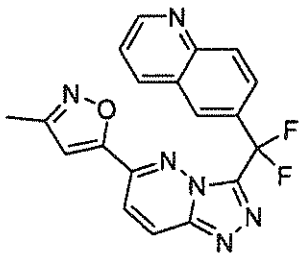
6-(1-(6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)ethyl)quinoline.

A solution of N'-(6-chloropyridazin-3-yl)-2-(quinolin-6-yl)propanehydrazide (2700 mg, 8238 µmol) in TFA (20 mL) was heated to 120 °C with microwaves (2 bar; 10 watts) for 40 min. The solution was concentrated under reduced pressure then partitioned between 9:1 CHCl3/IPA (75 mL) and 1 M NaOH (100 mL). The aqueous layer was further extracted with 9:1 $CHCl_3$/IPA (2x20 mL). The combined organics were dried over $MgSO_4$ then concentrated to an amber oil under reduced pressure. The product was isolated as off white crystaline solid from ACN. MS (ESI pos. ion) m/z: 310 (MH+). Calc'd exact mass for $C_{16}H_{12}ClN_5$: 309. Enantiomer resolved with: Chiralpak AD-H (3x25cm) column using 45% ethanol (0.1% DEA)/CO2

The following compounds were prepared using same method as *tert*-Butyl 2-(4-(3-(difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethylcarbamate and resolved from racemic mixtures:

Ex	Structure	MW	Mass Found	Peak #
485		355	356	1

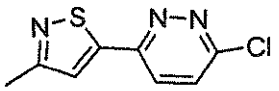
486		355	356	2
487		385	386	1
488		385	386	2
489		372	373	1
490		372	373	2



Example 491

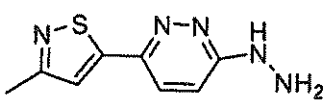
6-(difluoro(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline

A suspension of 1-(6-(3-methylisoxazol-5-yl)pyridazin-3-yl)hydrazine hydrochloride (200 mg, 879 μmol) and methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (208 mg, 879 μmol) in 5 M HCl (1 mL) was appropriately sealed and heated to 150 °C with microwaves for 4 h. The reaction was then quenched by a dropwise into cold 5 M NaOH (2 mL) and aqueous extracted with $CHCl_3$/IPA (25 mL). The organic phase was then dried over $MgSO_4$, concentrated, and purified with silica (40 g) eluting with 1>5% 2 M NH_3 in MeOH/DCM. The product was then further purified on RP-HPLC eluting with water/ACN (0.1% TFA). Combined fractions concentrated, dissolved in DCM (5 mL) and MeOH (5 mL), then stirred with Si-Carbonate (0.5 g; 35 mmol) for 1 h. Si-Carbonate removed by filtration and filtrated concentrated with <0.5 mL remaining with product isolated by trituration. MS (ESI pos. ion) m/z: 379 (MH+). Calc'd exact mass for $C_{19}H_{12}F_2N_6O$: 378.



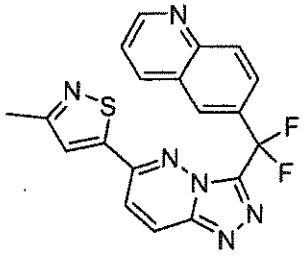
3-chloro-6-(3-methylisothiazol-5-yl)pyridazine

To a solution of 5-bromo-3-methylisothiazole (2.42 g, 14 mmol) in 20 mL of THF at -45 °C was added isopropylmagnesium chloride (19 ml, 19 mmol) in THF (1 M). After 20 minutes, zinc(II) chloride (41 ml, 20 mmol) in THF (0.5 M) was added and the solution was warmed up to rt. 3,6-dichloropyridazine (2.4 g, 16 mmol), 3,6-dichloropyridazine (2.4 g, 16 mmol) and Q-Phos (2.5 g) were added and the reaction was heated to 50 °C for 16 hours. The reaction was then cooled to 23 °C and quenched with 60 mL of satd. NH_4Cl aq. solution. The mixture was mixed with celite and 100 mL of EtOAc. The insoluble material was removed by filtration. The filtrate was diluted with 40 mL of EtOAc and 30 mL of water. The organic phase was separated and washed with 60 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (10% to 80% hex/EtOAc) to afford red solid as desired product. MS (ESI pos. ion) m/z: 212 (MH+). Calc'd exact mass for $C_8H_6ClN_3S$: 211.



1-(6-(3-methylisothiazol-5-yl)pyridazin-3-yl)hydrazine

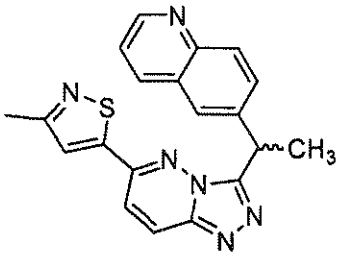
A mixture of 3-chloro-6-(3-methylisothiazol-5-yl)pyridazine (0.85 g, 4.0 mmol) and anhydrous hydrazine (3.8 ml, 120 mmol) in 30 mL of sec-BuOH was heated at 130 °C for 3 hours. The mixture was cooled to 23 °C and diluted with 5 mL of water. The solid was collected by filtration and was washed by 2 mL of water to produce a yellow solid. MS (ESI pos. ion) m/z: 208 (MH+). Calc'd exact mass for $C_8H_6ClN_3S$: 207.



Example 492

6-(difluoro(6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline

A mixture of methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (0.50 g, 2.1 mmol), 1-(6-(3-methylisothiazol-5-yl)pyridazin-3-yl)hydrazine (0.25 g, 1.2 mmol) and p-toluenesulfonic acid monohydrate (0.40 g, 2.1 mmol) in 5 mL of dioxane was heated at 150 °C for 1 hour in a microwave. The mixture was then diluted with 70 mL of EtOAc and 40 mL of satd. $NaHCO_3$ solution. The organic phase was separated and washed with 40 mL of brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by a silica gel column chromatography (EtOAc to 10% MeOH/EtOAc) to give yellow glass. The product was further purified by a prep-HPLC to give yellow glass. MS (ESI pos. ion) m/z: 395 (MH+). Calc'd exact mass for $C_{19}H_{12}F_2N_6S$: 394.

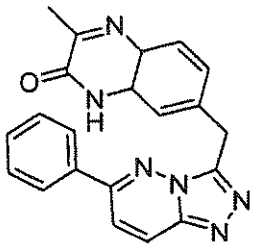


Example 493

6-(1-(6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)ethyl)quinoline

To a solution of 5-bromo-3-methylisothiazole (1.00 g, 5.6 mmol) in 10 mL of THF at -45 °C (CH_3CN/dry ice) was added isopropylmagnesium chloride LiCl complex (7.9 ml, 7.9 mmol) (LiCl complex, 1 M in THF). The mixture was stirred at -45 °C for 20 minutes and to this was added zinc chloride, 0.5 M in THF (17 ml, 8.4 mmol) slowly via a syringe. The mixture was

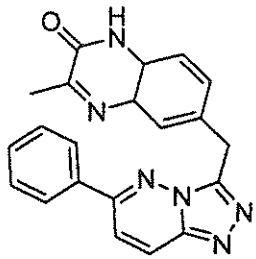
then warmed up to rt and continued to stir for additional 30 minutes. 6-(1-(6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)ethyl)quinoline (0.5787 g, 1.9 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.51 g, 0.56 mmol) and Q-Phos (0.65 g) in 15 mL of N,N-dimethyl acetamide was added to the reaction mixture. The reaction was warmed up to 50 °C for 6 hours and was quenched with 50 mL of satd. NH_4Cl aq. solution. The mixture was extracted with 150 mL of EtOAc and the organic phase was washed with 60 mL of brine. The aqueous phases were further extracted with 100 mL EtOAc. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (EtOAc to 15% MeOH in EtOAc) to give afford a red solid. MS (ESI pos. ion) m/z: 373 (MH+). Calc'd exact mass for $C_{20}H_{16}N_6S$: 372.



Example 494

3-methyl-6-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoxalin-2(1H)-one

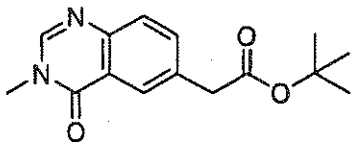
(See Example 495)



Example 495

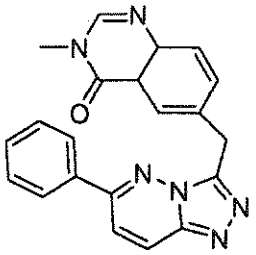
3-methyl-7-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoxalin-2(1H)-one.

A mixture of tert-butyl 2-(2-methyl-3-oxo-3,4-dihydroquinoxalin-6-yl)acetate (0.10 g, 0.36 mmol), tert-butyl 2-(3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)acetate (0.10 g, 0.36 mmol), 1-(6-phenylpyridazin-3-yl)hydrazine (0.081 g, 0.44 mmol) and p-toluenesulfonic acid monohydrate (0.069 g, 0.36 mmol) in 3 mL of dioxane was heated with microwave at 150 °C for 1 hour. The mixture was diluted with 70 mL of EtOAc and 40 mL of satd. $NaHCO_3$ solution. The organic phase was separated and was washed with 40 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to resolve the regiostereomers as example compounds 494 and 495. For each regiosteroemer MS (ESI pos. ion) m/z: 369 (MH+). Calc'd exact mass for $C_{21}H_{16}N_6O$: 368.



tert-butyl 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)acetate

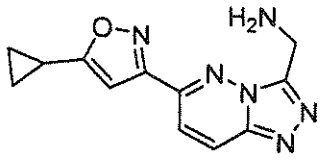
To a solution of 6-bromo-3-methylquinazolin-4(3H)-one (0.485 g, 2.0 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.19 g, 0.20 mmol) and Q-phos (0.20 g) in 40 mL of THF was added 2-tert-butoxy-2-oxoethylzinc chloride 0.5 M in diethyl ether (8.1 ml, 4.1 mmol). The reaction was heated at 50 °C for 16 hours and was quenched with 40 mL of satd. NH_4Cl. The mixture was diluted with 60 mL of EtOAc. The organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give red solid. The residue was purified by a silica gel column chromatography (5% EtOAc/Hex to EtOAC) to provide a red solid. MS (ESI pos. ion) m/z: 275 (MH+). Calc'd exact mass for $C_{15}H_{18}N_2O_3$: 274.



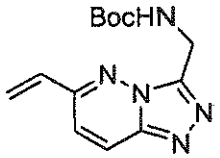
Example 496

3-Methyl-6-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinazolin-4(3H)-one:

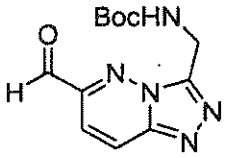
The title compound was prepared using the method for 3-methyl-6-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoxalin-2(1H)-one. MS (ESI pos. ion) m/z: 369 (MH+). Calc'd exact mass for $C_{21}H_{16}N_6O$: 368.



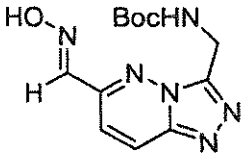
(6-(5-cyclopropylisoxazol-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methanamine



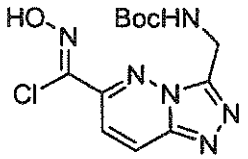
1) tert-butyl (6-vinyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. To an argon purged flask were added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (7.65 ml, 45.1 mmol), tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (3.20 g, 11.3 mmol), cesium carbonate (11.0 g, 33.8 mmol), and $PdCl_2(dppf)$-CH_2Cl_2 (0.461 g, 0.564 mmol). The mixture was dissolved in 38 mL of dioxane and 4 mL of water (0.25M 10:1) and was heated to 80 °C for 12 h. The mixture was cooled to room temperature, concentrated, and purified directly via MPLC (DCM/MeOH+1%NH_4OH)to afford the title compound (3.0 g, 95% yield).



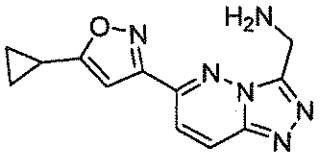
2) tert-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. Tert-butyl (6-vinyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (485 mg, 1.76 mmol) was dissolved in 5 mL of THF and 5 mL of water then osmium tetroxide (0.687 mL (4% water solution), 0.0176 mmol) was added and stirred for 5 min. Sodium periodate was added (141, 3.53 mmol) and the reaction was stirred for 2 h. The reaction was then extracted with dichloromethane (3 x 10 mL), dried over Na_2SO_4 and concentrated. Purification via MPLC (DCM/MeOH+1%NH_4OH) afforded title compound as a tan solid (350 mg, 72% yield).



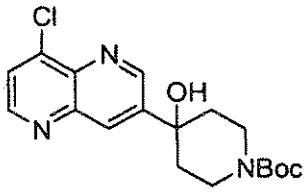
3) (E)-tert-butyl (6-((hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. Tert-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (400 mg, 1.44 mmol) and hydroxylamine hydrochloride (200 mg, 2.86 mmol) were combined in a flask with 25 mL of THF and 25 mL of 1 N NaOH solution. Stirred at rt for 1 h. Then added dichloromethane (50 mL) and extracted the aqueous layer 3 times with DCM (50 mL), dried over Na_2SO_4 and concentrated. Purified the oxime via MPLC (DCM/MeOH+1%NH_4OH) to give title compound (200 mg, 47% yield) as a tan solid.



4) (Z)-tert-butyl (6-(chloro(hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. Dissolved (E)-tert-butyl (6-((hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (200 mg, 0.684 mmol) in 25 mL of DMF and added 1-chloropyrrolidine-2,5-dione (95.9 mg, 0.718 mmol). Let stir at rt for 2 h. Poured reaction mixture onto water (20 mL) and extracted with ether (3 x 20 mL). Washed organics with water (2 x 20 mL), brine (1 x 20 ml), dried over sodium sulfate, filtered and concentrated. Title compound used without further purification (220 mg, 97% yield).

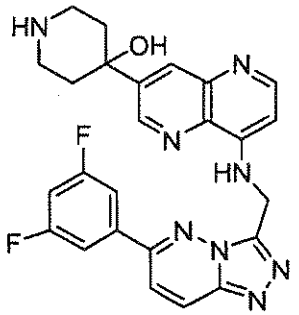


5) (6-(5-cyclopropylisoxazol-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methanamine. Dissolved (Z)-tert-butyl (6-(chloro(hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (110 mg, 337 μmol), ethynylcyclopropane (28 μl, 337 μmol), and potassium hydrogencarbonate (67.4 mg, 673 μmol) in 0.3 mL of EtOAc and heated to 60 °C for 12 h to afford the protected intermediate. The solvent was removed by rotary evaporation and the residue was redissolved in dicholoromethane (5 mL) and TFA (2 mL) and stirred for 30 min at room temperature. The solvent was then removed and the residue was redissolved in MeOH. Solid K_2CO_3 was added and the mixture was stirred for 1 h to free base the title compound. Purified the amine via MPLC (DCM/MeOH+1%NH_4OH) to afford the title compound(20 mg, 23% yield).



tert-butyl 4-(8-chloro-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate. Dissolved 3-bromo-8-chloro-1,5-naphthyridine (210 mg, 862 μmol) in 8 mL of THF and cooled to -78 °C. Then added butyllithium (517 μl, 1294 μmol) and stirred for 15 min. Added tert-butyl 4-oxopiperidine-1-carboxylate (258 mg, 1294 μmol) and let warm to room temperature over 1 h. The reaction was quenched with saturated NH_4Cl and extracted with dichloromethane (3 X 20 mL), dried over $NaSO_4$ and concentrated. Intermediate was purified

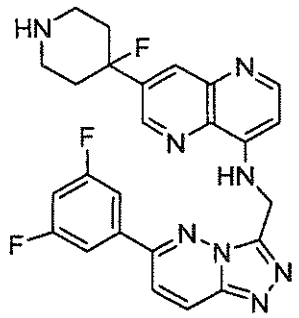
via MPLC (DCM/MeOH/NHOH) to yield tert-butyl 4-(8-chloro-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (120 mg, 38% yield.



Example 497

4-(8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yl)piperidin-4-ol.

Deprotection of tert-butyl 4-(8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate using the method described for (6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methanamine. M/Z = 489.2 [M+H], calc 488.19 for $C_{25}H_{22}F_2N_8O$.

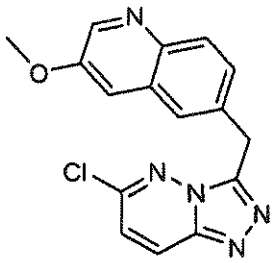


Example 498

N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(4-fluoropiperidin-4-yl)-1,5-naphthyridin-4-amine.

A solution of tert-butyl 4-(8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (30 mg, 51 μmol) in 0.5 mL of DCM was cooled to -78 C. Then added DAST (13 μl, 102 μmol) and let stir to room temperature over 30 min. TFA was then added to the reaction mixture and stirred for 30 min. The solvent was then removed by rotary evaporation and the residue was redissolved in MeOH and free based through a cation exchange column. Purification via MPLC

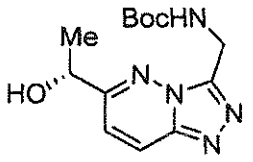
(DCM/MeOH+1%NH_4OH) yielded the title compound (15 mg, 60% yield). M/Z = 491.2 [M+H], calc 490.18 for $C_{25}H_{21}F_3N_8$.

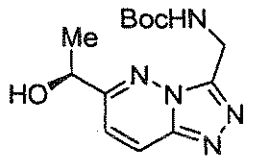


Example 499

6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-methoxyquinoline

To a 5 ml CEM microwave tube was added tert-butyl 2-(3-methoxyquinolin-6-yl)acetate (0.05 g, 0.2 mmol) , 1-(6-chloropyridazin-3-yl)hydrazine (0.04 g, 0.3 mmol), water (0.5 mL) and hydrochloric acid (0.05 ml, 0.5 mmol). The vial was sealed and first heated at 90 °C for 30 min then placed into CEM microwave for 10 min. at 100 °C, with 100 Watts of power via Powermax. The reaction mixture was adjusted the pH to 7 by adding 5 N NaOH - brown ppt. was generated. The brown ppt. was dissolved in DCM. The organic was washed with water, dried over $MgSO_4$, and removed solvent *in vacuo*. The crude product was purified using SiO_2 chromatography (Teledyne Isco RediSep®, P/N 68-2203-026, 12 g SiO_2, DCM:EtOAc:MeOH=75%:20%:5%, Flow = 30 mL/min). A peak at 25 min was collected. The solvent was removed *in vacuo* to afford the desired product as light yellowish solid. Wt: 20.0 mg. MS (ESI pos. ion) m/z: 326.53. Calc'd exact mass for $C_{16}H_{12}ClN_5O$: 325.75.

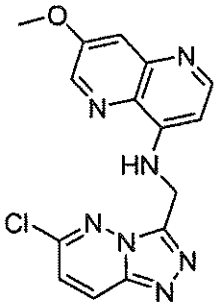




(*R/S*)-tert-butyl (6-(1-hydroxyethyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

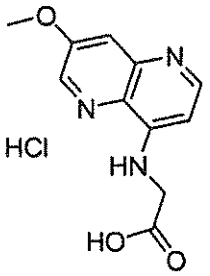
In a 10 mL round bottom flask under N_2 was dissolved *tert*-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (200 mg, 721 µmol) in 3 mL of THF then cooled at -78 °C and treated with methylmagnesium bromide (721 µl, 2164 µmol). After 30 minutes, the reaction mixture was warmed to 0 °C over 1h. After 1h the reaction mixture based on LC-MS was neutralized with NH_4Cl (sat.). The aqueous phase was extracted 3X with DCM then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The

crude tert-butyl (6-(1-hydroxyethyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (202 mg, 95.5% yield) was used without further purification in the next step. MS *m/z* = 294.4 $[M+1]^+$. Calc'd for $C_{13}H_{19}N_5O_3$: 293.3.



Example 500

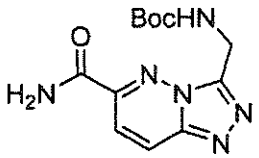
N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxyquinolin-4-amine.



a) 2-(7-methoxy-1,5-naphthyridin-4-ylamino)acetic acid hydrochloride. In a 100 mL round bottom flask were dissolved 8-chloro-3-methoxy-1,5-naphthyridine (5.00 g, 25.7 mmol) and glycine tert-butyl ester hydrochloride (17.2 g, 103 mmol) in 50 mL of 2-BuOH then stirred and heated at 100 °C. After 5h the solvent based on LC-MS was removed by reduced pressure and then the solid was dissolved in 200 mL of HCl 1N and stirred at 60 °C overnight. After 10h the reaction mixture based on LC-MS was cooled down to rt then 0°C and the desired acid precipitate. Filtered the solid (3.97 g) then evaporated the aqueous solution and triturated in 75 mL of H_2O at 0 °C then filter again and washed with 25 mL of H_2O at 0 °C (1.58 g) to afforded total 2-(7-methoxy-1,5-naphthyridin-4-ylamino)acetic acid hydrochloride (5.55 g, 80.1% yield) as a tan solid. MS *m/z* = 234.1 $[M+1]^+$. Calc'd for $C_{11}H_{11}N_3O_3$: 233.1.

b) N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine . In a 250 mL round bottom flask under N_2 were dissolved HATU (1762 mg, 4635 µmol), 1-(6-chloropyridazin-3-yl)hydrazine (536 mg, 3708 µmol), 2-(7-methoxy-1,5-naphthyridin-4-ylamino)acetic acid hydrochloride (1.00 g, 3708 µmol) in 25 mL of MeCN then stirred and cooled down at -40 °C then treated with TRIETHYLAMINE (2584 µl, 18540 µmol) and warmed to rt. After 30 min the reaction mixture based on LC-MS was evaporated

under reduced pressure and dry under high vacuum. The crude solid was dissolved in 100 mL of i-PrOH then treated with Ts-OH (2821 mg, 14832 μmol) and heated at 80 °C. After 3h the reaction mixture based on LC-MS was diluted with DCM then neutralized with NaOH (1N). The aqueous phase was extracted 3X with DCM with 10% MeOH then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was triturated with hot i-PrOH then cooled down and filtered (662 mg) and the mother liquor was evaporated under reduced pressure and purified by MPLC (ISCO) (210 mg) with DCM:MeOH 100:0 to 90:10 to afforded in combined yields N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine (872 mg, 69% yield) as a off-white solid. MS *m/z* = 342.1 $[M+1]^+$. Calc'd for $C_{15}H_{12}ClN_7O$: 341.7.



tert-Butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

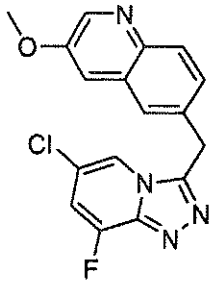
a) 3-((tert-butoxycarbonyl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid. In a 25 mL round bottom flask were dissolved 2-methyl-2-butene (21639 μl, 43278 μmol), potassium dihydrogen phosphate (2356 mg, 17311 μmol) and tert-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (600 mg, 2164 μmol) in 5 mL of *t*-BuOH and 5 mL of water then was added at 0 °C sodium chlorite (783 mg, 8656 μmol) and the reaction mixture was warmed to rt. After 10h the reaction mixture based on LC-MS was concentrated under reduced pressure and the crude acid was extract from the solid salts mixture with MeOH, filtered and the solvent was concentrated under reduced pressure. The crude 3-((tert-butoxycarbonyl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid (635 mg, 100% yield) was used without further purification in the next step. MS *m/z* = 294.2 $[M+1]^+$. Calc'd for $C_{12}H_{15}N_5O_4$: 293.1

b) tert-butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. In a 10 mL round bottom flask under N_2 were dissolved 3-((tert-butoxycarbonyl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid (250 mg, 852 μmol), HATU (389 mg, 1023 μmol), triethylamine (356 μl, 2557 μmol) in 1.5 mL of DMF then was treated with a (92 μl, 4262 μmol) and stirred at rt. After 2h the reaction mixture based on LC-MS was concentrated under reduced pressure and then purified by MPLC (ISCO) with DCM:MeOH+NH_4OH (1%) 100:0 to 90:10 to afforded tert-butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-

yl)methylcarbamate (129 mg, 52% yield). MS *m/z* = 293.2 $[M+1]^+$. Calc'd for $C_{12}H_{16}N_6O_3$: 292.3.

3-(aminomethyl)-N-methyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide.

The title compound was made using the same conditions as tert-butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate.

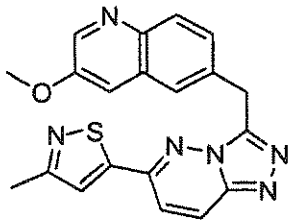


Example 501

6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline

a) 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine. A mixture of 5-chloro-2,3-difluoropyridine (10.0 g, 66.9 mmol) and hydrazine (10.0 ml, 319 mmol) in ^{i}PrOH (50 mL) was heated to 65 - 70 °C for 6 hours. The mixture was cooled to 23 °C, filtered, and washed with Na_2CO_3 (satd), and H_2O. Product isolated as a white solid. MS (ESI pos. ion) m/z: 162 (MH+). Calc'd exact mass for $C_5H_5ClFN_3$: 161.

b) 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinolin. To a mixture of 2-(3-methoxyquinolin-6-yl)acetic acid (0.22 g, 1.0 mmol), 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine (0.11 g, 0.68 mmol) and triphenylphosphine (0.97 g, 2.0 mmol) (on solid support) in DCM (5 mL) was added DIEA (0.24 ml, 1.4 mmol) followed by 2,2,2-trichloroacetonitrile (0.14 ml, 1.4 mmol) via a syringe. The mixture was then heated to 150 °C for 15 minutes in an appropriately sealed vial. The mixture was filtered and the filtrate was diluted with 50 mL of EtOAc. The solution was washed with 30 mL of satd. $NaHCO_3$ followed by 30 mL of brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by a silica gel column chromatography (EtOAc to 10% MeOH/EtOAc) to give light yellow solid as desired product. MS (ESI pos. ion) m/z: 343 (MH+). Calc'd exact mass for $C_{17}H_{12}ClFN_4O$: 342.

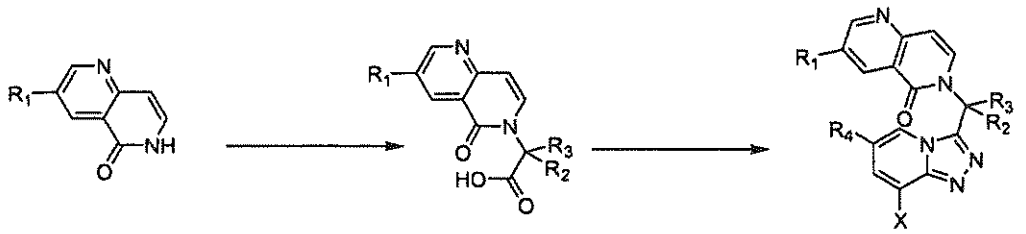


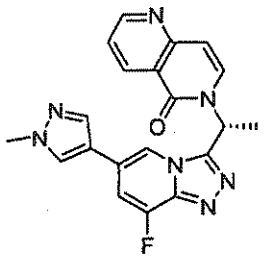
Example 502

3-Methoxy-6-((6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline

A flask charged with 5-bromo-3-methylisothiazole (0.049 g, 0.28 mmol) and 0.3 mL dry THF was cooled to 0 °C, and isopropylmagnesium chloride (0.30 ml, 0.30 mmol) added dropwise over 5 minutes and the mixture stirred an additional 5 minutes before allowing to warm to rt. The mixture was stirred at rt 10 minutes and the mixture cannulated to a solution of zinc(II) chloride (0.30 ml, 0.30 mmol) [1M] and the slurry stirred 10 minutes. The zincate was treated with 6-((6-iodo-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-methoxyquinoline (0.0890 g, 0.21 mmol), 1 mL dry THF, and a preformed solution of 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.012 g, 0.021 mmol) and Pd(OAc)2 (0.0024 g, 0.011 mmol) dissolved in 1 mL dry THF. The flask was fitted with a reflux condenser and heated with a 90 °C oil bath for 24 h. The zincate portion of this procedure was repeated, added to the reaction mixture, and the mixture heated at 90 °C for 1 h. The mixture was allowed to cool to rt and loaded onto 10 g of SiO_2 wet-packed with THF, and eluted with 200 mL THF. The eluents were concentrated *in vacuo*, and taken up in 5 mL EtOH. To the solution was added Si-sulfonic acid (1.5 g, 1.1 mmol) and the mixture stirred at room temperature for 24 h, and the solid collected. The solid was washed with EtOH (discarded), and then 2M NH_3 in EtOH (5 x 5 mL). The ammoniacal eluents were concentrated and the residue purified by HPLC to afford 3-methoxy-6-((6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline (0.0013 g, 1.6% yield).

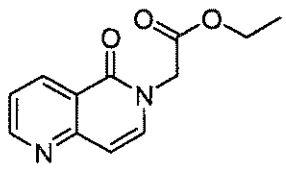
General Method N.





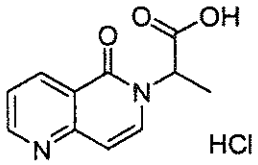
Example 503

(R)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one



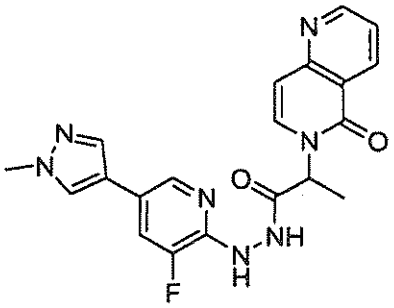
1. **ethyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)acetate.**

1,6-naphthyridin-5-ol (1.00 g, 6.8 mmol), ethyl iodoacetate (1.6 ml, 14 mmol) and cesium carbonate (4.5 g, 14 mmol) were dissolved in 25 mL of THF then stirred and heated at 100 °C for 2h until the reaction was complete. The reaction was concentrated and purified via MPLC using a gradient to 90% DCM : 10% MeOH to afford ethyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)acetate (1.5 g, 94% yield).



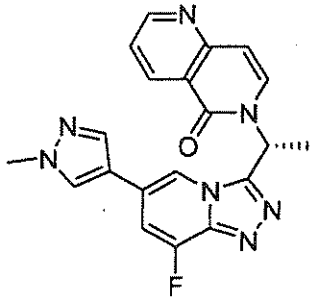
2. **2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.**

2-(5-oxo-1,6-naphthyridin-6(5H)-yl)acetate (32.0 g) was dissolved in 450 mL of a 6 N HCl solution, then stirred and heated at 100 °C for 1 hr until the reaction was complete. The reaction mixture was concentrated under reduced pressure, and azeotroped 3 times with benzene (200 mL) to remove the water. The crude 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (30.56 g, 92.3% yield) was used without further purification.



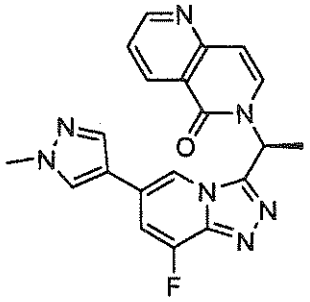
3. **N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide.**

HATU (1053 mg, 2.7 mmol), 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (470 mg, 1.8 mmol) and 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (421 mg, 2 mmol) (step 1 of General Method K) were taken up in 6 mL of acetonitrile. DIPEA (967 µl, 5.5 mmol) was added and the reaction was stirred for 30 minutes, until reaction was complete. The crude material was concentrated and then purified via MPLC with a gradient 100% DCM to 90% DCM / 10% MeOH / 1% NH_4OH) to yield N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (500 mg, 67% yield).



4. **(R)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

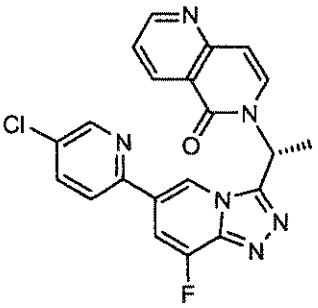
N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (400 mg, 982 µmol) and triphenylphosphine (386 mg, 1.4 mmol) were taken up in THF (9.8 mL). TMS-azide (195 µl, 1.4 mmol) was added, followed by slow addition of DEAD (233 µl, 1.4 mmol) and the reaction was stirred at room temperature for 1 hr until complete. The reaction was concentrated and purified via MPLC with a gradient 100 % DCM to 90% DCM / 10% MeOH / 1% NH_4OH to yield racemic 6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (220 mg, 57% yield) as a tan solid. Separated by preperative SFC (ChiralPak® OJ-H, (20 x 150 mm, 5 □m), 20% MeOH, 80% CO_2, 0.2% DEA; 100 bar system pressure; 70 mL/min; t_r : 3.5 min) to yield (R)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (60 mg, 15% yield). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS *m/z* = 390.2 [M+H], calc 389.14 for $C_{20}H_{16}FN_7O$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.16 (d, *J*=5.18 Hz, 3 H) 3.97 (s, 3 H) 6.82 (d, *J*=6.55 Hz, 1 H) 7.01 - 7.13 (m, 2 H) 7.41 - 7.49 (m, 1 H) 7.54 (d, *J*=6.26 Hz, 1 H) 7.61 (s, 1 H) 7.71 (s, 1 H) 8.33 (s, 1 H) 8.78 (d, *J*=7.73 Hz, 1 H) 8.93 (s, 1 H).



Example 504

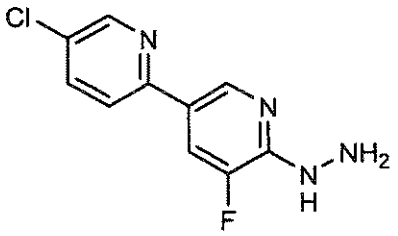
(S)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

The title compound was synthesized in the same general manner as that previously described for example 503. Seperated by preperative SFC (ChiralPak® OJ-H, (20 x 150 mm, 5 □m), 20% MeOH, 80% CO_2, 0.2% DEA; 100 bar system pressure; 70 mL/min; t_r : 4.3 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS *m/z* = 390.2 [M+H], calc 389.14 for $C_{20}H_{16}FN_7O$.

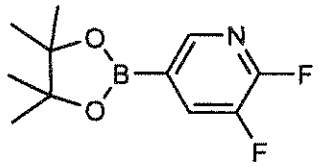


Example 505

(*R*)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

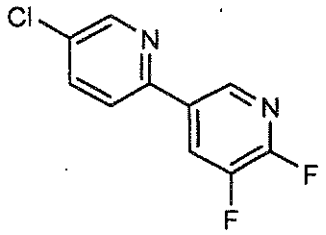


1. **1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine**



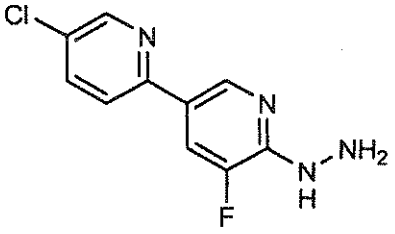
a. **2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine.**

A 350 mL resealable pressure vial was charged with 5-chloro-2,3-difluoropyridine (5.0 g, 33 mmol), pinacol diborane (13 g, 50 mmol), x-phos (1.9 g, 4.0 mmol), Pd_2dba_3 (1.8 g, 2.0 mmol), , and 1,4-dioxane (215 ml, 0.16 M), flushed with argon, sealed, then heated at 100°C for 16 hours. The mixture was concentrated and diluted with DCM (200 mL), then washed with water (50 mL). The organic layer was dried with $MgSO_4$, filtered, then concentrated to give a brown oil. The oil was purified by MPLC, eluting with 10-60% EtOAc/Hexanes. 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.6 g, 69% yield) was isolated as a light orange oil which solidified upon standing. LC/MS shows the product as the boronic acid. However, the structure of the product is as drawn above. MS m/z = 160.2 $[M+1]^+$. Calc'd for $C_{11}H_{14}BF_2NO_2$: 241.0



b. **5-(5-chloropyridin-2-yl)-2,3-difluoropyridine.**

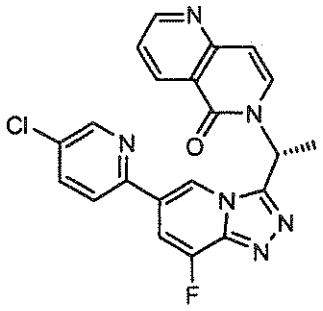
To a pressure vessel was added 2-bromo-5-chloropyridine (3.0 g, 16 mmol), cesium carbonate (15 g, 47 mmol), 1,1'-bis (diphenylphosphino)ferrocene-palladium(ii) dichloride dichloromethane complex (2.5 g, 3.1 mmol), and 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (4.5 g, 19 mmol) in 1,4-dioxane (120 mL) and water (22 mL). The mixture was flushed with argon, sealed and stirred at 90°C for three hours. The mixture was concentrated, diluted with dichloromethane and washed with water. Organic extracts were concentrated and purified by MPLC (eluted with 0-10% methanol in dichloromethane) to yield 5-(5-chloropyridin-2-yl)-2,3-difluoropyridine as a yellow solid (2.4 g, 68%). MS m/z = 227.2 $[M+1]^+$. Calc'd for $C_{10}H_5ClF_2N_2$: 226.6.



c. **1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine.**

To a solution of 5-(5-chloropyridin-2-yl)-2,3-difluoropyridine (2.4 g, 11 mmol) in IPA (35 mL, 0.3 M) at room temperature was added hydrazine (4 mL, 127 mmol). The reaction mixture was stirred at 60°C for 2 h, at which point the reaction was cooled to room temperature and concentrated in vacuo. The concentrated material was suspended in saturated $NaHCO_3$ and

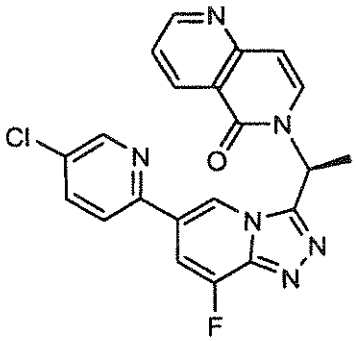
filtered to obtain product as a white, fluffy solid. The material was re-suspended in water (30 mL), and filtered to obtain 1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine (2.1 g, 83% yield). MS m/z = 239.2 $[M+1]^+$. Calc'd for $C_{10}H_8ClFN_4$: 238.6.



2. **(R)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one**

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 150 mm 5m), 30% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 4.0mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer.

MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{14}ClFN_6O$: 420.8. 1H NMR (400 MHz, DMSO-d_6) □ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 6.78 (d, *J*=7.82 Hz, 1 H) 7.03 (d, *J*=6.94 Hz, 1 H) 7.54 (dd, *J*=8.07, 4.55 Hz, 1 H) 7.78 (d, *J*=7.82 Hz, 1 H) 7.97 - 8.09 (m, 2 H) 8.16 (dd, *J*=8.56, 2.49 Hz, 1 H) 8.61 (dd, *J*=7.97, 1.71 Hz, 1 H) 8.70 - 8.78 (m, 1 H) 8.92 (dd, *J*=4.55, 1.81 Hz, 1 H) 9.03 (d, 1 H).

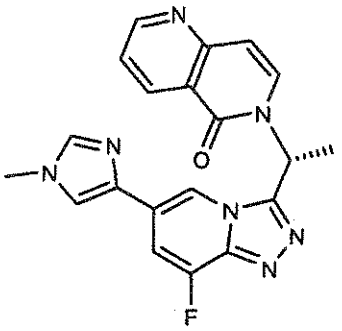


Example 506

(S)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

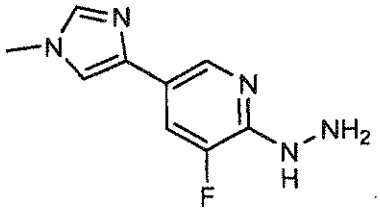
Prepared in the same general manner as that previously described for example 505 using General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 150 mm 5m), 30% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 5.8 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the

same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{14}ClFN_6O$: 420.8.



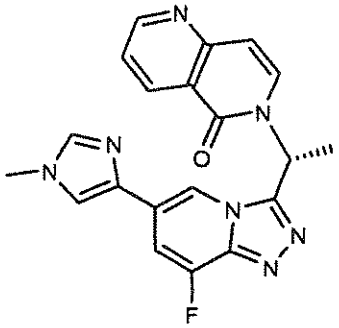
Example 507

***(R)*-6-(1-(8-fluoro-6-(1-methyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one**



1. **1-(3-fluoro-5-(1-methyl-1H-imidazol-4-yl)pyridin-2-yl)hydrazine**

Prepared in the same general manner as that previously described for 1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine

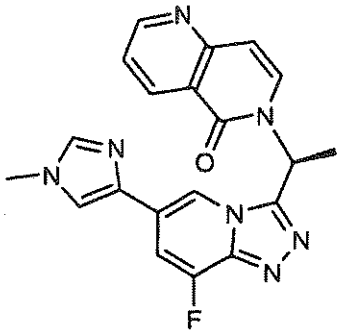


2. ***(R)*-6-(1-(8-fluoro-6-(1-methyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r 4.1mins).

On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 389.8 $[M+1]^+$. Calc'd for $C_{20}H_{16}FN_7O$: 389.4. 1H NMR (400 MHz, DMSO-d_6) □ ppm 1.97 (d, *J*=6.94 Hz, 3 H) 3.68 (s, 3 H) 6.75 (d, *J*=7.73 Hz, 1 H) 6.94 (d, *J*=6.85 Hz, 1 H) 7.52 -

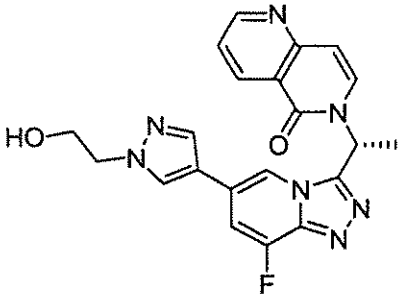
7.59 (m, 1 H) 7.64 (dd, *J*=7.78, 0.54 Hz, 1 H) 7.69 - 7.75 (m, 3 H) 8.46 (s, 1 H) 8.63 (dt, *J*=8.12, 0.88 Hz, 1 H) 8.90 - 8.94 (m, 1 H)



Example 508

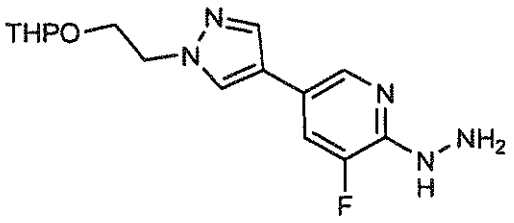
(S)-6-(1-(8-fluoro-6-(1-methyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

Prepared in the same general manner as that previously described for example 507 using General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 5.9 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 389.8 $[M+1]^+$. Calc'd for $C_{20}H_{16}FN_7O$: 389.4 .

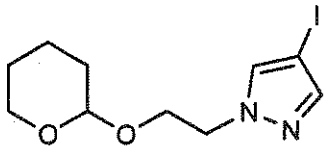


Example 509

(R)-6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

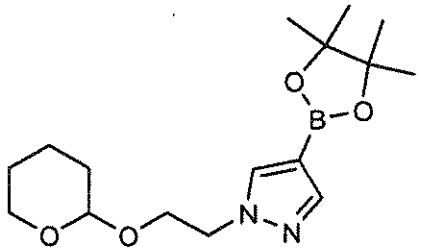


1. **1-(3-fluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine**



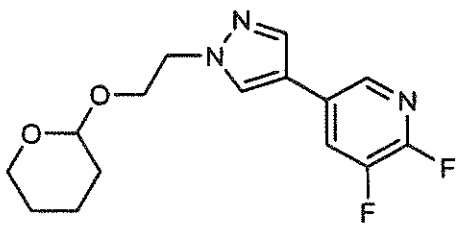
a. **4-iodo-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole.**

A mixture of cesium carbonate (20.7 g, 63.4 mmol) and 4-iodopyrazole (10.00 g, 51.6 mmol) in DMF (100 mL) was allowed to stir for 10 min. To the mixture was added 2-(2-bromoethoxy)tetrahydro-2h-pyran (9.98 ml, 63.4 mmol) and heated at 80°C overnight. The mixture was diluted with water and extracted with EtOAc (3 x 50 mL), and subsequently washed with water (2 x 50 mL) and brine, dried over sodium sulfate, and filtered. The crude mixture was evaporated onto silica gel and purified via MPLC (0% to 50%; EtOAc in hexanes). Isolated 4-iodo-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole (15.3 g, 92%) as a clear oil. MS m/z = 323.0 $[M+1]^+$. Calc'd for $C_{10}H_{15}IN_2$: 322.1.



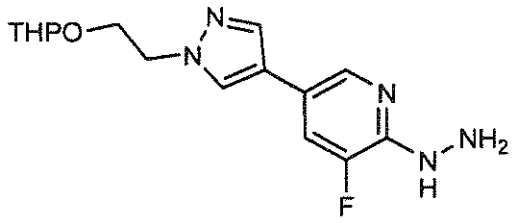
b. **1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.**

To a solution of 4-iodo-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole (8.7 g, 27.1 mmol) in THF (75 mL) at 0°C under argon was added isopropylmagnesium chloride as a 2 M solution in THF (27.1 mL, 54.3 mmol). The reaction was stirred for 1h at 0°C. To it was added 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.7 mL, 40.7 mmol) and the mixture was stirred for an additional 1 h while allowing to warm to room temperature. It was then treated with saturated ammonium chloride (100 mL) solution and the product was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over sodium sulfate, and filtered. Crude material was concentrated under reduced pressure to afford 7.1 g (81%) of 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as a clear yellow oil. The material was taken on crude to the next step. MS m/z = 323.2 $[M+1]^+$. Calc'd for $C_{16}H_{27}BN_2O_4$: 322.2



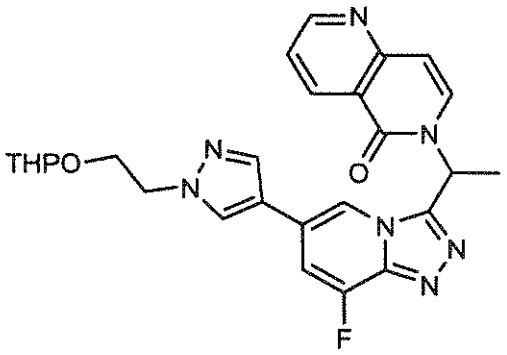
c. **2,3-difluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridine.**

A 48 mL tube was charged with 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (6.4 g, 19.9 mmol), 5-chloro-2,3-difluoropyridine (1.7 mL, 16.6 mmol), X-Phos (1.6 g, 3.3 mmol), Potassium phosphate (3.5 g, 16.6 mmol), $PdOAc_2$ (0.4 g, 1.7 mmol), 1,4-dioxane (50 mL), and water (5.0 mL), flushed with argon, sealed, then heated at 100°C for 3 hours. The mixture was concentrated and purified by MPLC, eluting with 2.5% MeOH/DCM over 40 minutes to afford 2,3-difluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridine as a clear oil which solidified upon standing at room temperature (3.1 g, 60.5% yield). LC/MS shows the product as the free alcohol. However, the structure of the product is as drawn above. MS m/z = 226.2 $[M+1]^+$. Calc'd for $C_{15}H_{17}F_2N_3O_2$: 309.3



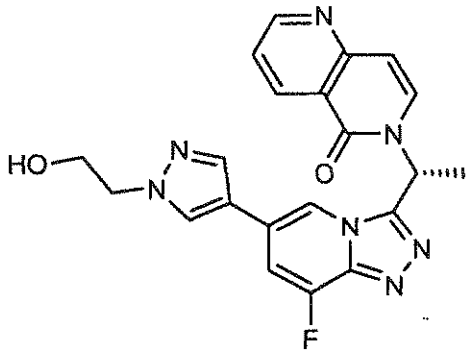
d. **1-(3-fluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine.**

To a solution of 2,3-difluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridine (3.0 g, 9.5 mmol) in IPA (47.7 mL, 0.2 M) at room temperature was added hydrazine (3.6 mL, 114.4 mmol). The reaction mixture was stirred at 60 °C for 2 h, at which point the reaction was cooled to room temperature and concentrated in vacuo. The concentrated material was suspended in saturated $NaHCO_3$ solution and filtered to obtain product as a white, fluffy solid. The material was re-suspended in water (30 mL), filtered, and driend under high vacuum to obtain 1-(3-fluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (2.2 g, 72% yield) as an orange solid. MS m/z = 322.2 $[M+1]^+$. Calc'd for $C_{15}H_{20}FN_5O_2$: 321.4.



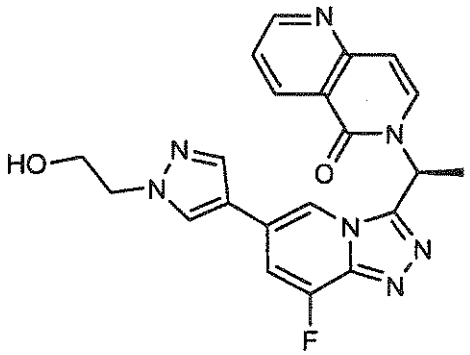
2. **6-(1-(8-fluoro-6-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

The THP-protected compound was synthesized according to the General Method N.



3. **(R)-6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

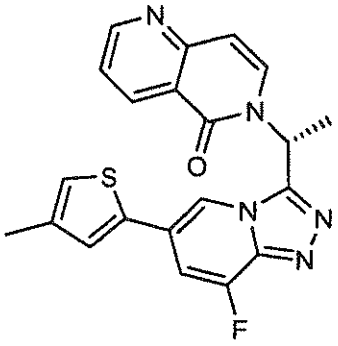
6-(1-(8-fluoro-6-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (0.5 g, 1.0 mmol) was dissolved in EtOH (12 mL) and to the solution was added hydrochloric acid (2.0 mL, 4.0 mmol). The reaction was stirred at rt for 3 hours at which time it was diluted with 5 mL of water and 10 mL of aq. saturated sodium bicarbonate solution. The product was extracted with DCM (30mL) three times. The organic layers were combined, dried over sodium sulfate and concentrated to dryness to afford 6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (0.4 g, 96%). Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 m, 5□m), 35% EtOH, 65% CO2, 0.2 DEA; 100 bar system pressure, 50 mL/min; t_r :4.4 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 420.2 [M+H], calc 419.15 for $C_{21}H_{18}FN_7O_2$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 4.00 - 4.09 (m, 2 H) 4.29 - 4.33 (m, 2 H) 6.91 (d, *J*=7.92 Hz, 1 H) 7.04 (dd, 1 H) 7.10 (dd, *J*=10.56, 1.17 Hz, 1 H) 7.51 (dd, *J*=8.17, 4.74 Hz, 1 H) 7.59 (d, *J*=7.82 Hz, 1 H) 7.72 (d, *J*=0.68 Hz, 1 H) 7.76 (d, *J*=0.78 Hz, 1 H) 8.34 (d, *J*=1.17 Hz, 1 H) 8.84 (dd, *J*=8.07, 1.22 Hz, 1 H) 8.92 (dd, *J*=4.74, 1.81 Hz, 1 H)



Example 510

(S)-6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

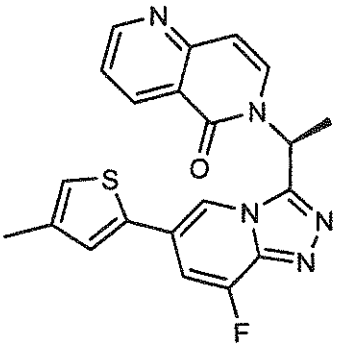
Prepared in the same general manner as that previously described for example 509 using General Method N. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 m, 5□m), 35% EtOH, 65% CO2, 0.2 DEA; 100 bar system pressure, 50 mL/min; t_r :6.0 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 420.2 [M+H], calc 419.15 for $C_{21}H_{18}FN_7O_2$.



Example 511

(R)-6-(1-(8-fluoro-6-(4-methylthiophen-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

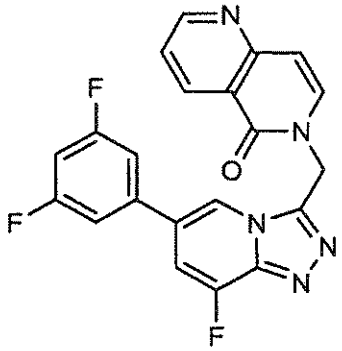
The compound was prepared according to General Method N. The hydrazine was prepared in an analogous fashion to 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 80 mL/min and 100bar system backpressure, retention time = 5.1 minutes. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the R enantiomer. MS m/z = 406.0 $[M+1]^+$. Calc'd for $C_{21}H_{16}FN_5OS$: 405.5.



Example 512

(S)-6-(1-(8-fluoro-6-(4-methylthiophen-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

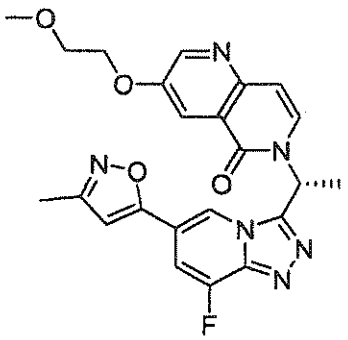
The compound was prepared according to General Method N. The hydrazine was prepared in an analogous fashion to 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 80 mL/min and 100bar system backpressure, retention time = 6.1 minutes. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the S enantiomer. MS m/z = 406.0 $[M+1]^+$. Calc'd for $C_{21}H_{16}FN_5OS$: 405.5.



Example 513

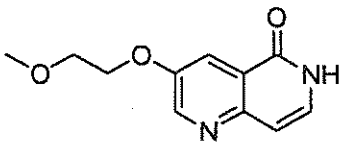
6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-1,6-naphthyridin-5(6H)-one

The title compound was synthesized in the same general manner as that previously described for example 503 using 1-(5-(3,5-difluorophenyl)-3-fluoropyridin-2-yl)hydrazine. MS *m/z* = 408.2 [M+H], calc 407.4for $C_{21}H_{12}F3N_5O$.

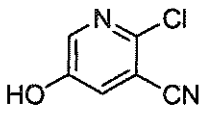


Example 514

(R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one

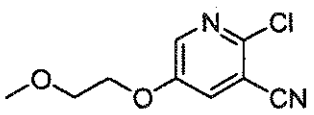


1. **3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one**



a. **2-chloro-5-hydroxynicotinonitrile.**

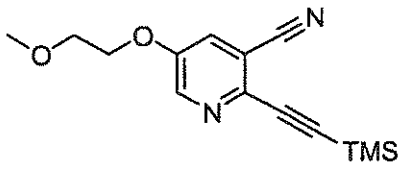
In a 300 mL sealed tube under N_2 were dissolved potassium acetate (20 g, 207 mmol), 5-bromo-2-chloronicotinonitrile (15 g, 69 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (21 g, 83 mmol) and $PdCl_2(dppf)$-CH_2Cl_2 Adduct (1.7 g, 2.1 mmol) in 150 mL of p-dioxane then stirred and heated at 85 °C for 2 hrs. After completion, the reaction was cooled to 0 °C and treated with hydrogen peroxide (31.5%) (22 ml, 207 mmol) then stirred at rt for 1 hr. The reaction mixture was diluted with DCM (100 mL) then water was added (200 mL). The aqueous phase was extracted 3 times with DCM (100 mL), then the organic layer was washed with saturated sodium thiosulfate solution (300 mL). The organics were then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude 2-chloro-5-hydroxynicotinonitrile (7.5 g, 70% yield) was carried through crude to the next step.



b. **2-chloro-5-(2-methoxyethoxy)nicotinonitrile.**

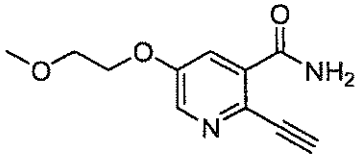
In a 100 mL round bottom flask under N_2 were dissolved triphenylphosphine (19 g, 73 mmol),

2-chloro-5-hydroxynicotinonitrile (7.5 g, 49 mmol), and 2-methoxyethanol (5.7 ml, 73 mmol) in THF (130 mL) followed by a slow addition of DEAD (27 ml, 68 mmol), and then stirred at room temperature. After 2h the reaction showed full conversion to the desired compound. The crude mixture was purified by MPLC eluting with 100% DCM to 90% DCM:10% MeOH to afford 2-chloro-5-(2-methoxyethoxy)nicotinonitrile (6.46 g, 63% yield) as a tan solid.



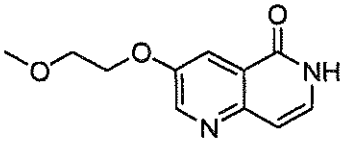
c. **5-(2-methoxyethoxy)-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile.**

In a sealed tube, dichlorobis(triphenyl-phosphine)palladium (ii) (0.17 g, 0.24 mmol), trimethylacetylene (2.0 ml, 14 mmol), 2-chloro-5-(2-methoxyethoxy)nicotinonitrile (2.50 g, 12 mmol), and copper(I) iodide (0.11 g, 0.59 mmol) were dissolved in acetonitrile (0.5 M, 24 mL) and to the reaction was added triethylamine (3.3 ml, 24 mmol). The reaction mixture was heated to 85 °C for 12 hrs. The reaction was concentrated and purified directly via MPLC, eluting with 0-100% EtOAc in hexanes to yield 5-(2-methoxyethoxy)-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile (1.9 g, 59% yield).



d. **2-ethynyl-5-(2-methoxyethoxy)nicotinamide.**

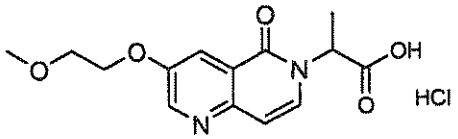
5-(2-methoxyethoxy)-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile (4.23 g, 15 mmol) was dissolved in acetone (60 mL). To the solution was added 3 M sodium carbonate (62 ml, 185 mmol) and hydrogen peroxide (31 ml, 308 mmol) dropwise, and it was stirred at room temperature for 4 h. After completion, the reaction was cooled to 0 °C and to it was slowly added sodium thiosulfate (200 mL) with stirring. The aqueous layer was extracted with DCM (x3, 200 mL), and the combined organics were concentrated and purified via MPLC eluting with 100% DCM to 90% DCM:10% MeOH:1% NH_4OH to yield 2-ethynyl-5-(2-methoxyethoxy)nicotinamide (2.0 g, 59% yield).



e. **3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one.**

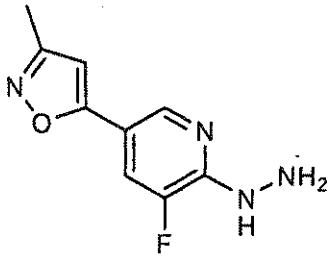
2-ethynyl-5-(2-methoxyethoxy)nicotinamide (2.04 g, 9 mmol) was dissolved in 1M dimethylamine (in methanol or ethanol) (46 ml, 93 mmol). The reaction was heated to 85 °C

for 12 hrs. The reaction was concentrated and purified via MPLC eluting with 100% DCM to 90% DCM:10% MeOH:1% NH_4OH to yield 3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one (0.900 g, 44% yield).

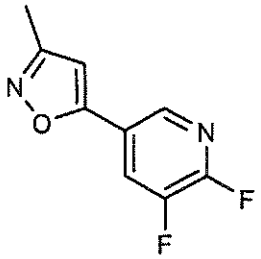


2. **2-(3-(2-methoxyethoxy)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.**

The compound was synthesized from 3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one similar to the synthesis of 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride in Method N (Example 503).

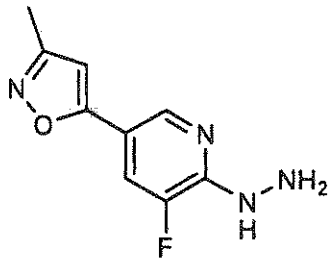


3. **1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine**



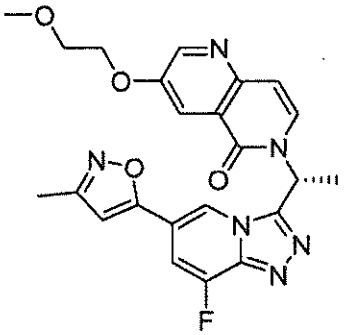
a. **2,3-difluoro-5-(3-methylisoxazol-5-yl)pyridine.**

A 330 mL pressure vessel was charged with 5-chloro-2,3-difluoropyridine (5.00 g, 33.4 mmol), 3-methyl-5-(tributylstannyl)isoxazole (14.9 g, 40.1 mmol), XPhos (2.23 g, 4.68 mmol), $PdOAc_2$ (0.526 g, 2.34 mmol), and 1,4-dioxane (167 ml, 33.4 mmol), flushed with argon, sealed, then heated at 100°C for 16 hours. The mixture was concentrated; the black oil was absorbed onto silica gel and purified by MPLC, eluting with 20% EtOAc in hexanes isocratic to yield an orange solid; this was triturated with hexanes to give 2,3-difluoro-5-(3-methylisoxazol-5-yl)pyridine (3.6278 g, 55.3% yield) as a yellow solid.



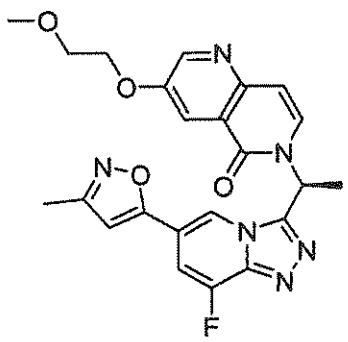
b. 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine.

A 330 mL pressure vessel was charged with 4,5-difluoro-2-(3-methylisoxazol-5-yl)pyridine (3.6695 g, 18.7 mmol), hydrazine (3.53 ml, 112 mmol), and IPA (93.5 ml, 18.7 mmol), sealed, then heated at 65°C for 3 hours. The mixture was filtered; the solid was triturated with sat. aqueous $NaHCO_3$ solution and washed with water (2 x 20 mL). 1-(4-fluoro-6-(3-methylisoxazol-5-yl)pyridin-3-yl)hydrazine (3.5668 g, 91.6% yield) was isolated as a white powder.



4. (R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one.

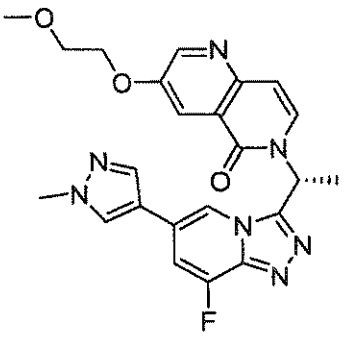
Using 3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one and 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine, the title compound was synthesized using General Method N to yield (R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 mm, 5□m), 25% MeOH, 75% CO_2, 0.2% DEA; 100 bar system pressure; 75 mL/min; t_r 5.78 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 465.2 [M+H], calc 464.16 for $C_{23}H_{21}FN_6O_4$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 2.39 (s, 3 H) 3.49 (s, 3 H) 3.78 - 3.94 (m, 2 H) 4.23 - 4.43 (m, 2 H) 6.43 (s, 1 H) 6.85 (d, *J*=7.82 Hz, 1 H) 7.08 (q, *J*=7.11 Hz, 1 H) 7.29 (dd, *J*=10.07, 1.17 Hz, 1 H) 7.43 (d, *J*=7.82 Hz, 1 H) 8.17 (d, *J*=2.93 Hz, 1 H) 8.58 - 8.81 (m, 2 H).



Example 515

(S)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one

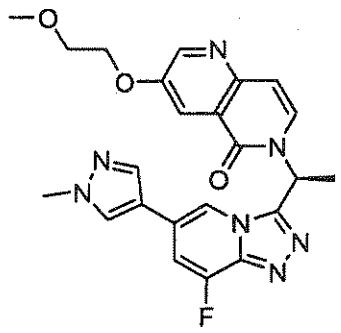
Synthesized in the same general manner as that previously described for example 509 using General Method N. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 mm, 5□m), 25% MeOH, 75% CO_2, 0.2% DEA; 100 bar system pressure; 75 mL/min; t_r 4.75min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 465.2 [M+H], calc 464.16 for $C_{23}H_{21}FN_6O_4$



Example 516

(*R*)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one

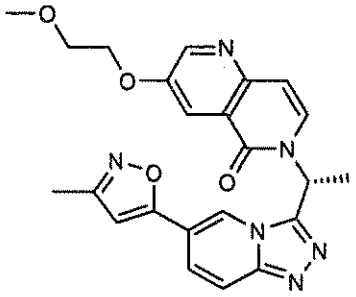
The title compound was synthesized using General Method N. Chiral separation by preparative SFC (Chiralpak® AS-H (20 x 150 mm, 5 □m), 20% iPrOH, 80% CO_2; 100 bar system pressure, 50 mL/min; t_r 1.67 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 464.2 [M+H], calc 463.18 for $C_{23}H_{22}FN_7O_3$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.15 (d, *J*=7.14 Hz, 3 H) 3.49 (s, 3 H) 3.80 - 3.90 (m, 2 H) 3.97 (s, 3 H) 4.27 - 4.39 (m, 2 H) 6.83 (d, *J*=7.73 Hz, 1 H) 7.00 - 7.13 (m, 2 H) 7.42 (d, *J*=7.82 Hz, 1 H) 7.61 (s, 1 H) 7.72 (s, 1 H) 8.15 (d, *J*=2.84 Hz, 1 H) 8.31 (s, 1 H) 8.72 (d, *J*=3.03 Hz, 1 H).



Example 517

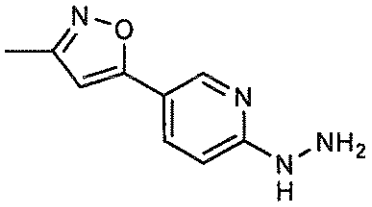
(*S*)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one

The compound was synthesized in the same general manner as that previously described for example 516 according to General Method N. Chiral separation by preparative SFC (Chiralpak® AS-H (20 x 150 mm, 5 □m), 20% iPrOH, 80% CO_2; 100 bar system pressure, 50 mL/min; t_r : 2.02 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 464.2 [M+H], calc 463.18 for $C_{23}H_{22}FN_7O_3$.

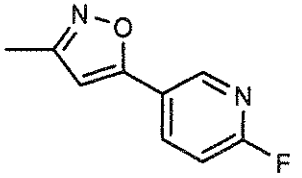


Example 518

(R)-3-(2-methoxyethoxy)-6-(1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

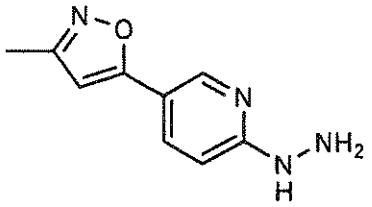


1. 1-(5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine



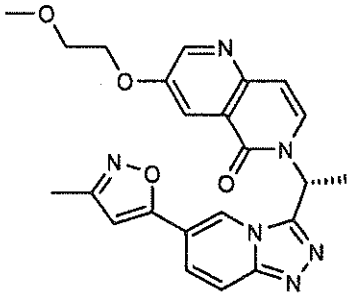
a. 2-fluoro-5-(3-methylisoxazol-5-yl)pyridine.

A 48 mL tube tube was charged with 5-bromo-2-fluoropyridine (1.17 ml, 11.4 mmol), 3-methyl-5-(tributylstannyl)isoxazole (5.29 g, 14.2 mmol), cyclohexyl JohnPhos (0.398 g, 1.14 mmol), Pd_2dba_3 (0.312 g, 0.341 mmol), and DMF (12.4 ml, 159 mmol), flushed with argon, sealed, then heated at 90°C for 16 hours. Additional 3-methyl-5-(tributylstannyl)isoxazole (5.29 g, 14.2 mmol) (2 g), Pd_2dba_3 (0.312 g, 0.341 mmol), and cyclohexyl JohnPhos (0.398 g, 1.14 mmol) were added and the mixture was stirred at 90°C for 10 more hours. This was concentrated and the brown residue was purified by MPLC, eluting with 15% ethyl acetate in hexanes isocratic. 2-fluoro-5-(3-methylisoxazol-5-yl)pyridine (1.1029 g, 54.5% yield) isolated as a light yellow solid.



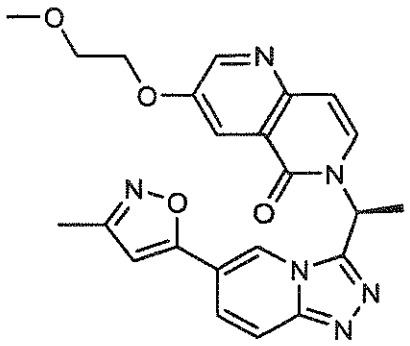
b. <u>1-(5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine.</u>

The hydrazine was synthesized similar to 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine (except heated to 60°C) (84.2% yield).



2. <u>(R)-3-(2-methoxyethoxy)-6-(1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.</u>

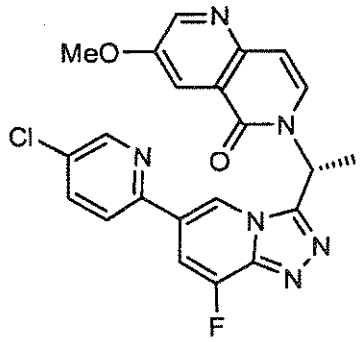
The title compound was synthesized according to General Method N. Chiral separation by preparative SFC (Chiralcel OH-H (2 cm ID x 25 cm length, 5 μ), 35 – 65% MeOH 0.2% DEA in CO_2, 80 mL/min; t_r = 4.95 min). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 447.2 $[M+1]^+$. Calc'd for $C_{23}H_{22}N_6O_4$: 446.5. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (t, 1 H), 8.68 (d, *J*=3.03 Hz, 1 H), 8.01 - 8.02 (m, 1 H), 7.96 (dd, *J*=9.59, 1.08 Hz, 1 H), 7.79 (dd, *J*=9.54, 1.61 Hz, 1 H), 7.60 (d, *J*=7.82 Hz, 1 H), 7.01 - 7.05 (m, 1 H), 6.99 (s, 1 H), 6.75 (d, *J*=7.63 Hz, 1 H), 4.29 - 4.32 (m, 2 H), 3.70 - 3.73 (m, 2 H), 3.32 (s, 3 H), 2.31 (s, 3 H), 1.99 (d, *J*=7.04 Hz, 3 H).



Example 519

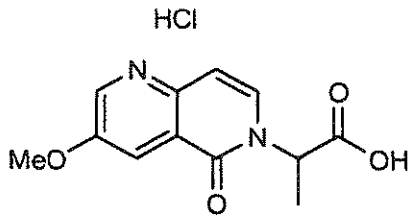
(S)-3-(2-methoxyethoxy)-6-(1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

Compound was synthesized in the same general manner as that previously described for example 518 according to General Method N. Chiral separation by preparative SFC (Chiralcel OH-H (2 cm ID x 25 cm length, 5 μ), 35 – 65% MeOH 0.2% DEA in CO_2, 80 mL/min; t_r = 7.05 min). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 447.2 $[M+1]^+$. Calc'd for $C_{23}H_{22}N_6O_4$: 446.5.



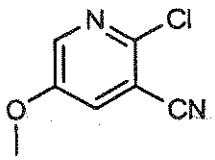
Example 520

***(R)*-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one**



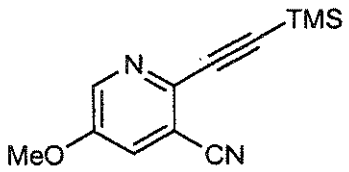
1. 2-(3-methoxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride

All steps for the synthesis of this acid are the same as for 2-(3-(2-methoxyethoxy)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (Example 514). with the following exceptions:



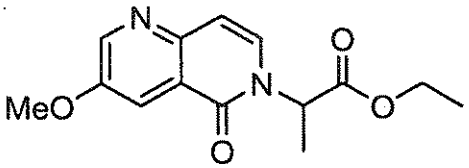
a. **2-chloro-5-methoxynicotinonitrile.**

2-chloro-5-hydroxynicotinonitrile (18.0 g, 116 mmol) was placed in a resealable pressure-resistant tube and suspended in DMF (146 ml, 116 mmol). To this was added cesium carbonate (76 g, 233 mmol) and methyl iodide (36 mL, 582 mmol). The vessel was sealed and the mixture stirred at 65 ^{0}C for 17 h. The reaction mixture was diluted with water (250 mL) and the product was extracted with DCM (3 X400mL). The organic layers were combined, dried over sodium sulfate and concentrated to afford 40g of brown thick oil. This was passed through a plug of silica to afford 13g of 85% pure material. This was triturated in 10%DCM/Hexanes (hot ~ 40^{0}C) and solids filtered, rinsed with hexanes and dried to afford 2-chloro-5-methoxynicotinonitrile as brown solid (10.0 g, 51%). MS m/z = 169[M+1]$^+$. Calc'd for $C_7H_5ClN_2O$: 168.6.



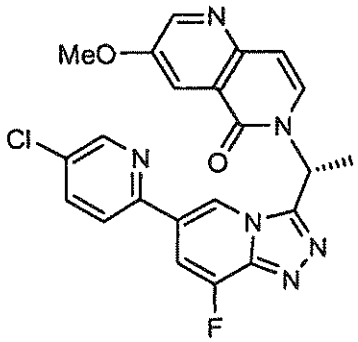
b. **5-methoxy-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile.**

This step was run at 65°C instead of 85°C.



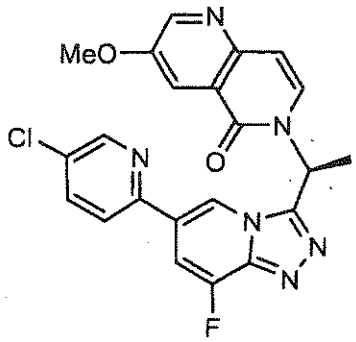
c. **ethyl 2-(3-methoxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate.**

Ethyl 2-bromopropanoate was used instead of the iodide and the reaction temperature was also lower (60^{0}C).



2. **(R)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one.**

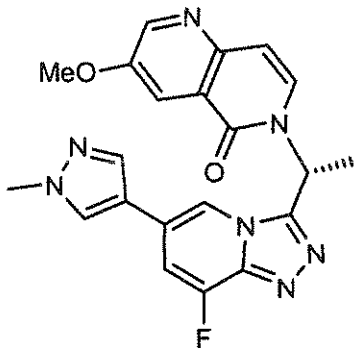
The title compound was synthesized according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 35% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 6.3 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 450.8 $[M+1]^+$. Calc'd for $C_{22}H_{16}ClFN_6O_2$: 450.8.



Example 521

(S)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 35% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 8.0 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. m/z = 450.8 $[M+1]^+$. Calc'd for $C_{22}H_{16}ClFN_6O_2$: 450.8.

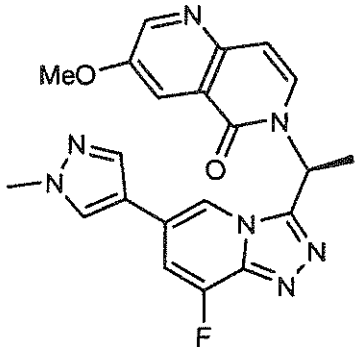


Example 522

***(R)*-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one**

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 40% EtOH 0.2% DEA, 70 mL/min and 100bar system backpressure

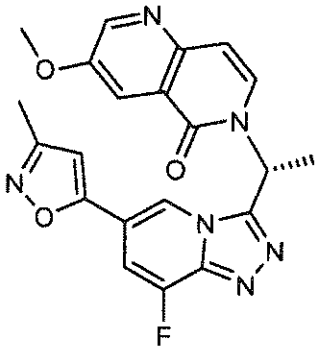
(t_r: 5.2 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 419.8 $[M+1]^+$. Calc'd for $C_{21}H_{18}FN_7O_2$: 419.4.



Example 523

(*S*)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 40% EtOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 6.8 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 419.8 $[M+1]^+$. Calc'd for $C_{21}H_{18}FN_7O_2$: 419.4.

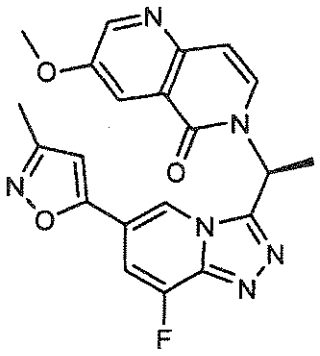


Example 524

(*R*)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 4.7 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{17}FN_6O_3$: 420.4. 1H NMR (400 MHz, DMSO-d_6) □ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.94 (s, 3 H)

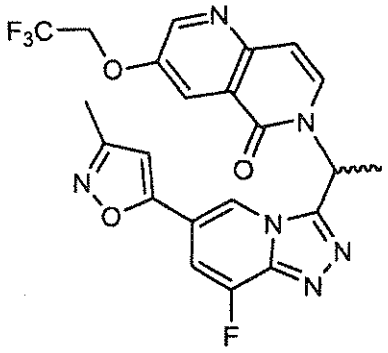
6.77 (dd, *J*=7.78, 0.54 Hz, 1 H) 6.94 - 7.05 (m, 2 H) 7.64 (d, *J*=7.82 Hz, 1 H) 7.76 - 7.89 (m, 1 H) 7.98 (dd, *J*=3.08, 0.54 Hz, 1 H) 8.68 (d, *J*=3.03 Hz, 1 H) 8.80 (d, *J*=1.08 Hz, 1 H).



Example 525

(*S*)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

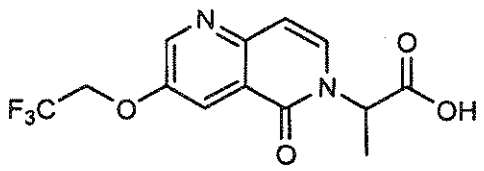
Prepared according to General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 3.9 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{17}FN_6O_3$: 420.4.



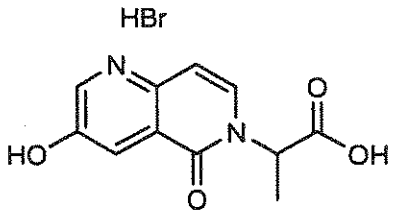
Example 526

6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-5(6H)-one

HCl

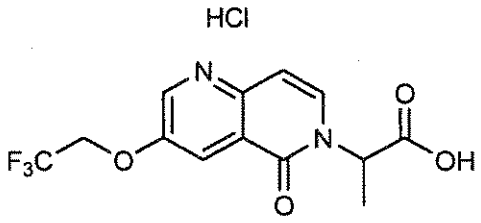


1. **2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride**



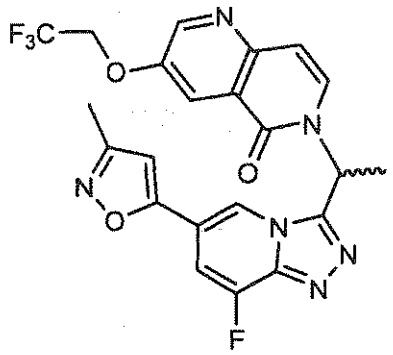
a. **2-(3-hydroxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrobromide.**

A resealable pressure-resistant bottle was charged with ethyl 2-(3-methoxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate (0.83 g, 3.0 mmol) (Example 515) and conc. HBr (0.16 ml, 3.0 mmol). The vessel was sealed and the mixture was stirred at 130^{0}C for 20 hours. The reaction mixture was then concentrated to afford 2-(3-hydroxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrobromide (0.95 g, 100% yield) as brown solid. This was carried through crude in the next step. Free base material MS m/z = 235.0 $[M+1]^+$. Calc'd for $C_{11}H_{11}BrN_2O_4$: 315.1.



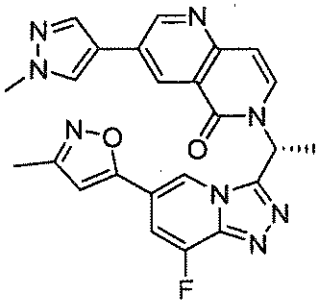
b. **2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.**

A resealable pressurized vial was charged with 2-(3-hydroxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrobromide (0.54 g, 2 mmol), cesium carbonate (2 g, 7 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (2 g, 7 mmol), and N,N-dimethylformamide (6 mL, 0.3M). The vessel was sealed and the mixture was stirred at 60^{0}C fo 1 hr. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was collected, dried over sodium sulfate, and concentrated under reduced pressure to afford brown oil. This was purified via MPLC (10-50% EtOAC/Hexanes) to afford tan solid of bis alkylated material. This was suspended and refluxed in 5 mL of 6N HCl for 2 hours. Reaction mixture concentrated and dried under reduced pressure to afford 2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (0.3 g, 50% yield). This was concentrated under reduced pressure to dryness to afford 2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (0.3 g, 50% yield) as yellow solid. Free base material MS m/z = 317.0 $[M+1]^+$. Calc'd for $C_{13}H_{12}ClF_3N_2O_4$: 352.7.



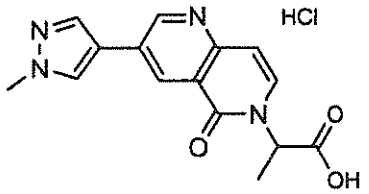
2. **6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-5(6H)-one.**

Prepared according to General Method N. MS m/z = 488.8 $[M+1]^+$. Calc'd for $C_{22}H_{16}F_4N_6O_3$: 488.4. 1H NMR (400 MHz, DMSO-d_6) □ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.25 - 2.38 (m, 3 H) 5.05 (q, *J*=8.77 Hz, 2 H) 6.74 - 6.83 (m, 1 H) 6.96 - 7.07 (m, 2 H) 7.71 (d, *J*=7.82 Hz, 1 H) 7.86 (dd, *J*=11.49, 1.12 Hz, 1 H) 8.20 (d, *J*=2.74 Hz, 1 H) 8.78 (d, *J*=3.03 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H)



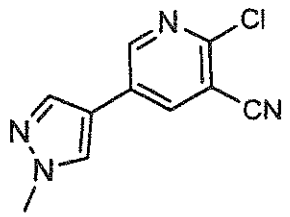
Example 527

6-((R)-1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)-1,6-naphthyridin-5(6H)-one



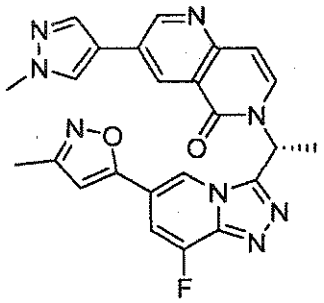
1. **2-(3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride**

All steps for the synthesis of this acid are the same as for 2-(3-(2-methoxyethoxy)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (Example 514) with the following exception:



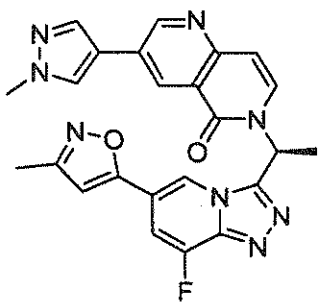
a. 2-chloro-5-(1-methyl-1H-pyrazol-4-yl)nicotinonitrile.

A 48 mL tube was charged with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.42 g, 40.5 mmol), 5-bromo-2-chloronicotinonitrile (8.00 g, 36.8 mmol), potassium carbonate (15.3 g, 110 mmol), $PdCl_2(dppf)$ (2.69 g, 3.68 mmol), 1,4-dioxane (135 mL, 1582 mmol) and water (23.9 mL, 1324 mmol), flushed with argon, sealed and then heated to 60°C for 8 h. The reaction mixture was concentrated, adsorbed onto silica gel, and purified via MPLC eluting with 3% MeOH in DCM. 2-chloro-5-(1-methyl-1H-pyrazol-4-yl)nicotinonitrile (4.962 g, 61.7%) was obtained (with a small impurity). The material was taken forward crude.



2. 6-((R)-1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)-1,6-naphthyridin-5(6H)-one.

Synthesized using General Method N. Chiral separation by preparative SFC (Chiralpak® OJ-H 5 □m (20 x 250 mm, 5 □m), 45% MeOH, 55%, CO_2, 0.2% DEA, 70 mL/min; 120 bar system pressure; t_r : 8.3 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 471.2 [M+H], calc 470.16 for $C_{24}H_{19}FN_8O_2$. ^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.89 (s, 3 H) 6.78 (d, *J*=8.41 Hz, 1 H) 6.95 - 7.09 (m, 2 H) 7.72 (d, *J*=7.82 Hz, 1 H) 7.85 (d, *J*=12.62 Hz, 1 H) 8.12 (s, 1 H) 8.46 (s, 1 H) 8.67 (dd, *J*=2.35, 0.68 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H) 9.20 (d, *J*=2.45 Hz, 1 H).

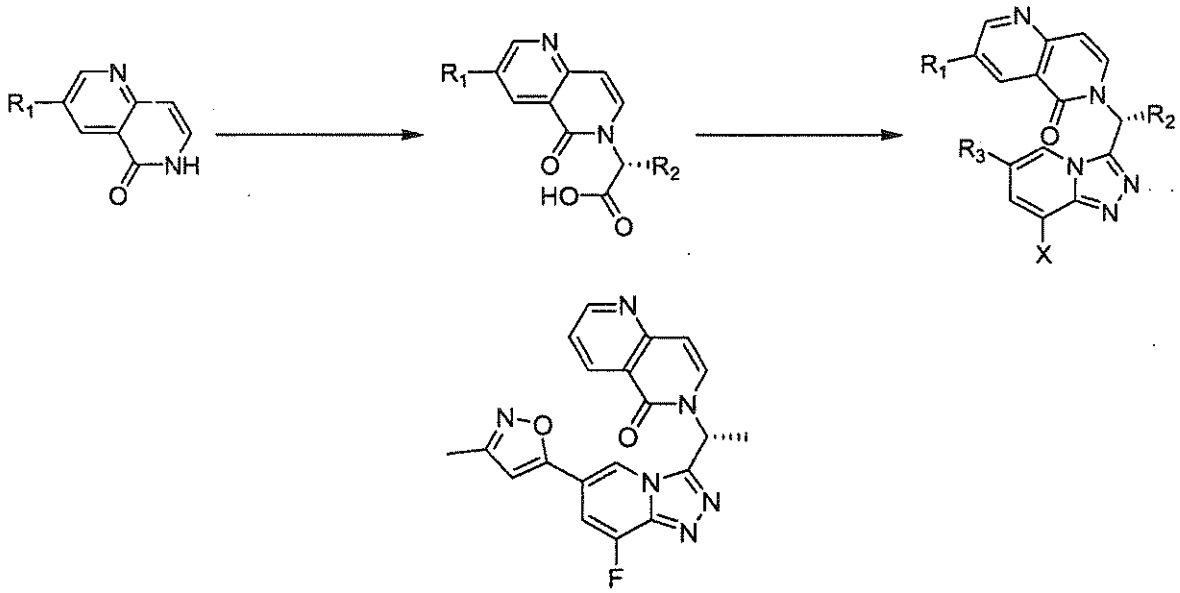


Example 528

6-((*S*)-1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)-1,6-naphthyridin-5(6H)-one

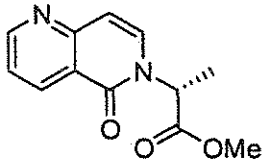
Prepared in the same general manner as that previously described for example 527 according to General Method N. Chiral separation by preparative SFC (Chiralpak® OJ-H 5 □m (20 x 250 mm, 5 □m), 45% MeOH, 55%, CO_2, 0.2% DEA, 70 mL/min; 120 bar system pressure; t_r : 7.2 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 471.2 [M+H], calc 470.16 for $C_{24}H_{19}FN_8O_2$.

General Method O.



Example 529

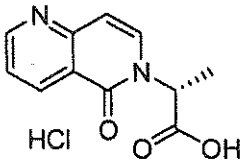
(R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one



1. (R)-methyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate.

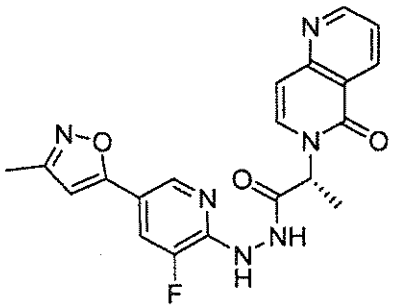
Dissolved 1,6-naphthyridin-5(6H)-one (10.6 g, 73 mmol), (S)-methyl 2-hydroxypropanoate (8.6 ml, 91 mmol) and triphenylphosphine (30 g, 116 mmol) in 144 mL THF (0.5M) and cooled to 0 °C. Then added DEAD (17 ml, 109 mmol) dropwise, monitoring temperature so as not to exceed 5 °C. Then let warm to room temperature over 1 hr, where reaction was complete by LCMS. The reaction was concentrated on silica and purified via MPLC, first with a gradient of Hexanes:EtOAc (removes most of PPh_3O); then gradient of 100% DCM to 90%

DCM:10% MeOH:1% NH_4OH to yield (R)-methyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate (16 g, 95% yield) where the ee was confirmed to be >95%.



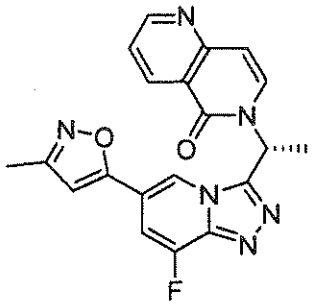
2. **(R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.**

Dissolved (R)-methyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate (3.20 g, 14 mmol) in 70 mL of THF and added 6 M HCl (23 ml, 138 mmol) and heated to 80 °C for 3 hrs until reaction was complete by LCMS. Reaction concentrated to remove water, and azeotroped 3 times with benzene to remove excess water, to yield (R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (3.4 g, 95% yield) which was >95% ee according to HPLC (conditions: 25/75 EtOH-TFA (0.1%):Heptane, ChiralPak AD-H, 1.0 mL/min, 20 min, 4.6X150 mm column). Obtained (R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride as a yellow solid, which was taken on crude to the next step.



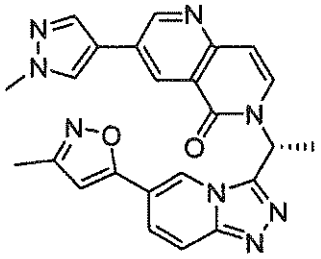
3. **(2R)-N'-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide.**

HATU (9.0 g, 24 mmol), (R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride and 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine (3.6 g, 17 mmol) were taken up in acetonitrile (52 ml, 0.3 M) and cooled to 0 °C. DIPEA (8.2 ml, 47 mmol) was added dropwise and the reaction was allowed to stir to room temperature for 30 minutes until complete by LCMS. The crude material was concentrated onto silica gel and then purified via MPLC eluting with 100% DCM to 90% DCM:10% MeOH:1% NH_4OH to yield (2R)-N'-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (4.927 g, 77% yield).



4. **(R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

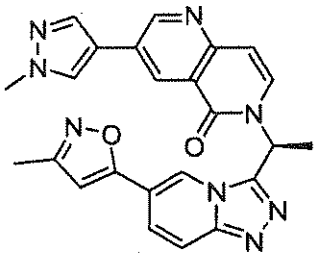
(2R)-N'-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (1.9 g, 4.7 mmol) and triphenylphosphine (1.8 g, 7.0 mmol) were taken up in THF (47 ml, 4.7 mmol). TMS-azide (0.93 ml, 7.0 mmol) was added, followed by slow addition of DEAD (1.1 ml, 7.0 mmol) and the reaction was stirred at room temperature for 50 minutes (monitored temperature so as not too exceed 30-40 °C) until reaction was complete. The reaction mixture was concentrated down, removing approximately ½ volume of THF. The material was then redissolved in EtOAc (~100 mL), and 2 M HCl (~30 mL) was added. The mixture was shaken vigorously, and the aqueous layer (with product) was set aside. The EtOAc layer was extracted x2 with HCl (30 mL) and all of the aqueous layers were combined. The aqueous layer was cooled to 0 °C, and to it was added 6 M NaOH dropwise until pH was 7-8 (desired product crashed out as an off-white solid). The solid was filtered over vacuum to remove desired product from water. The solid was then dissolved through the frit into a new flask with DCM/MeOH, and dried over $NaSO_4$ (to further dry). The product was then recrystallized from EtOH with heat, sonication and then cooling or scratching to promote rapid crystallization. (R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (1.5 g, 60-80% yield) was isolated as a white solid with >95% ee by HPLC (conditions: 50/50 EtOH:Heptane, ChiralPak® AD-H, 1.0 mL/min, 20 min, 4.6X150 mm column, tr 6.61 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 391.2 [M+H], calc 390.12 for $C_{20}H_{15}FN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 6.78 (d, *J*=7.92 Hz, 1 H) 6.95 - 7.12 (m, 2 H) 7.54 (dd, *J*=8.22, 4.50 Hz, 1 H) 7.77 (d, *J*=7.73 Hz, 1 H) 7.85 (d, *J*=11.54 Hz, 1 H) 8.62 (d, *J*=9.59 Hz, 1 H) 8.82 (s, 1 H) 8.92 (dd, *J*=4.55, 1.71 Hz, 1 H).



Example 530

3-(1-methyl-1H-pyrazol-4-yl)-6-((R)-1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

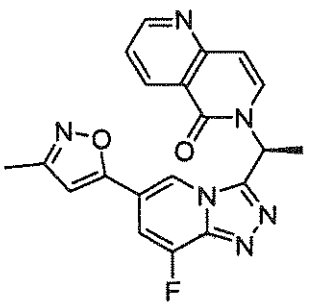
Prepared in the same general manner as that previously described for example 527 according to General Method N. Chiral separation by preparative SFC (ChiralCel OD-H (20 x 250 mm 5□), 35:65:0.2 MeOH:CO_2:DEA, 80 mL/min and 100 bar system backpressure (t_r: 12 mins).. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 453.0 [M+H], calc 452.5 for $C_{24}H_{20}N_8O_2$.



Example 531

3-(1-methyl-1H-pyrazol-4-yl)-6-((S)-1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

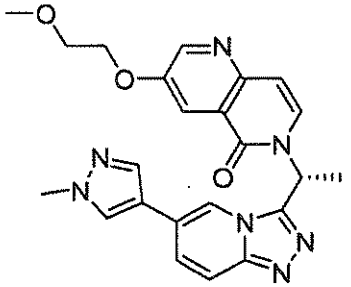
Prepared in the same general manner as that previously described for example 527 according to General Method N. Chiral separation by preparative SFC (ChiralCel OD-H (20 x 250 mm 5□), 35:65:0.2 MeOH:CO_2:DEA, 80 mL/min and 100 bar system backpressure (t_r: 18 mins).. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 453.0 [M+H], calc 452.5 for $C_{24}H_{20}N_8O_2$.



Example 532

(S)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

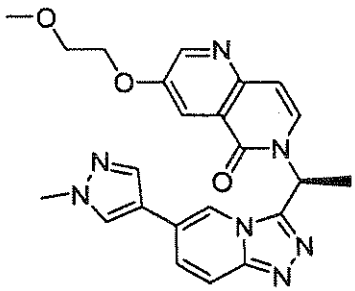
Synthesized according to General Method N. Seperated by preperative HPLC (ChiralPak® IA, (50 x 250 mm, 5 □m), 50% Heptane, 50% EtOH; 100 mL/min; t_r : 14.0 min) to yield (S)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 391.2 [M+H], calc 390.12 for $C_{20}H_{15}FN_6O_2$.



Example 533

(R)-3-(2-methoxyethoxy)-6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

Synthesized using General Method N. Chiral separation by preparative SFC (Chiralpak® OD-H (20 x 250 mm, 5 □m), 30% MeOH, 70%, CO_2, 0.2% DEA, 70 mL/min; 100 bar system pressure; t_r : 6.8 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 446.2 [M+H], calc 445.19 for $C_{23}H_{23}N_7O_3$.

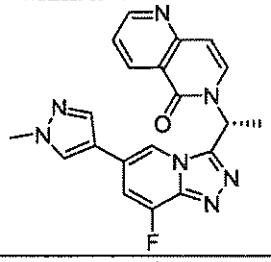
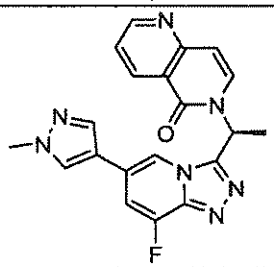
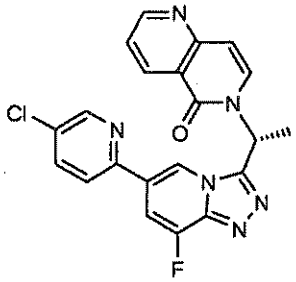
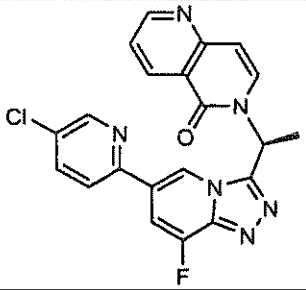
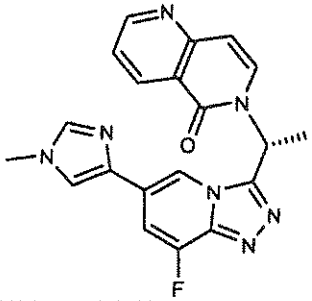


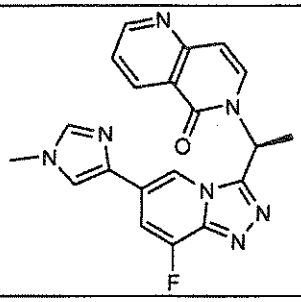
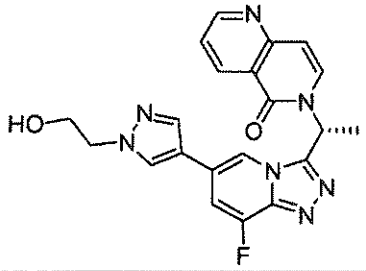
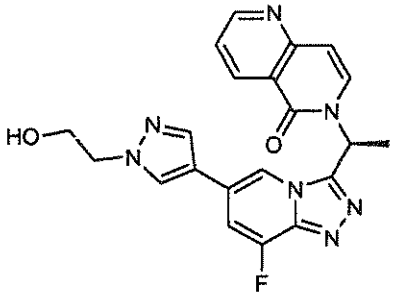
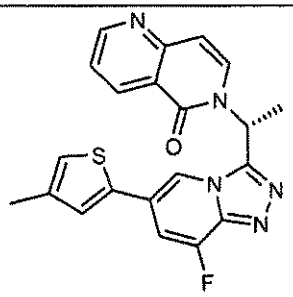
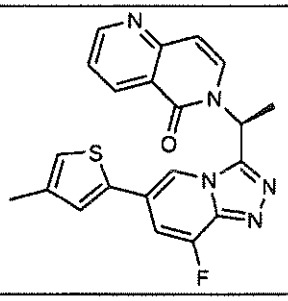
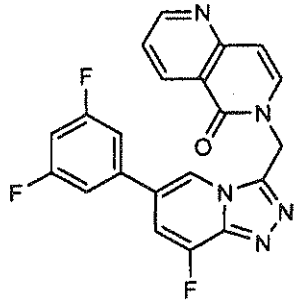
Example 534

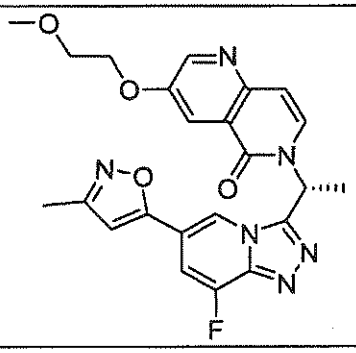
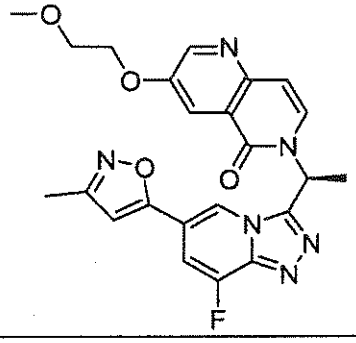
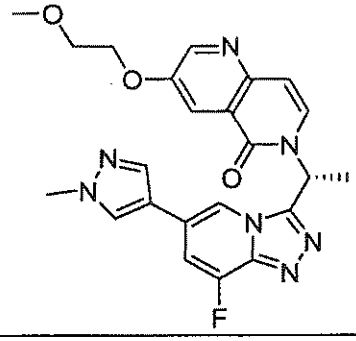
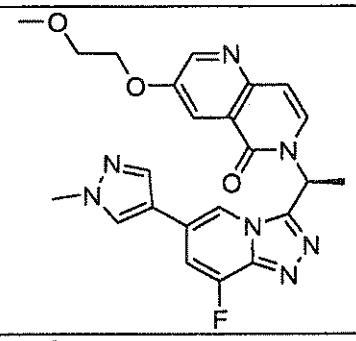
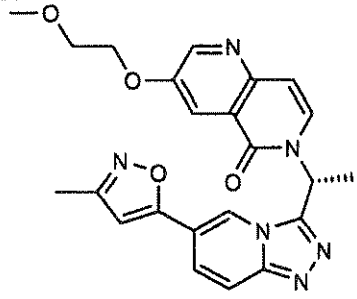
(S)-3-(2-methoxyethoxy)-6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

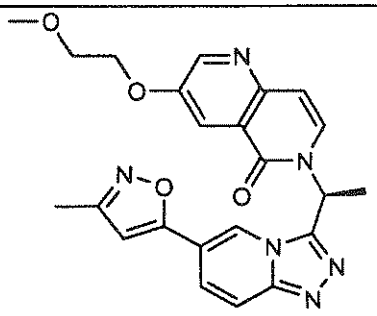
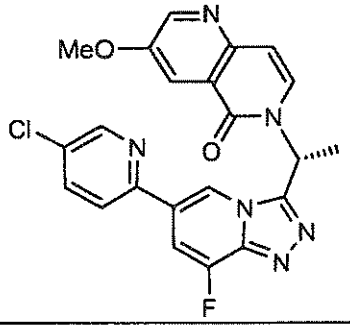
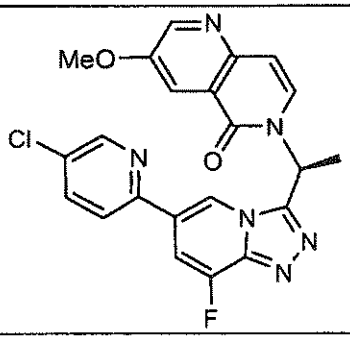
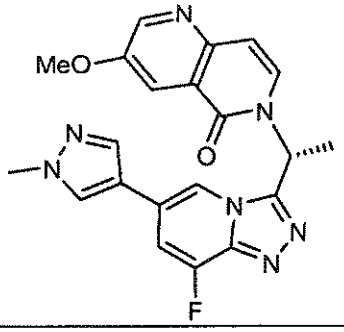
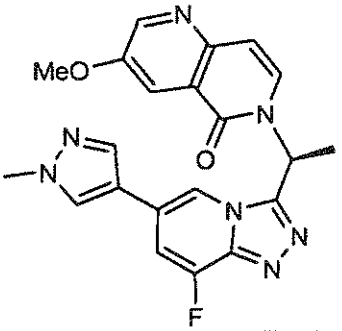
Prepared in the same general manner as that previously described for example 533 according to General Method N. Chiral separation by preparative SFC (Chiralpak® OD-H (20 x 250 mm, 5

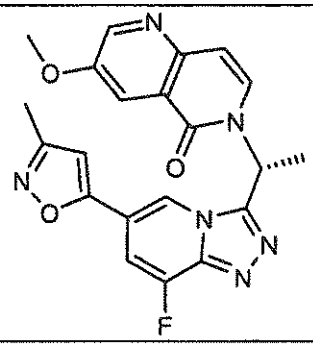
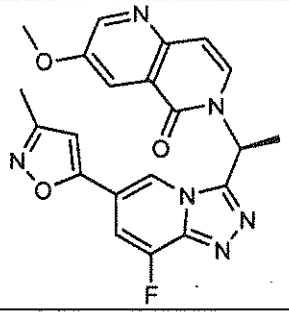
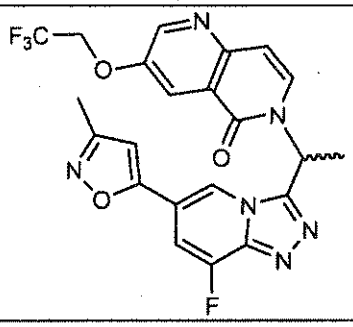
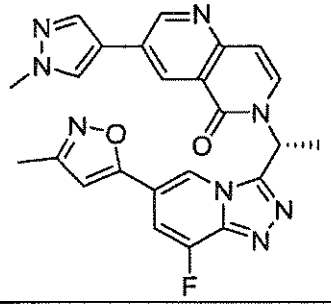
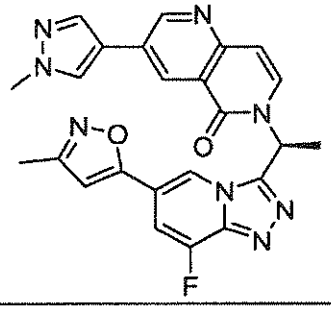
□m), 30% MeOH, 70%, CO_2, 0.2% DEA, 70 mL/min; 100 bar system pressure; t_r : 9.9 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 446.2 [M+H], calc 445.19 for $C_{23}H_{23}N_7O_3$.

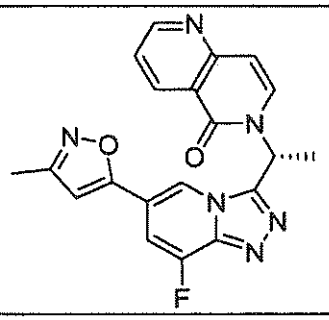
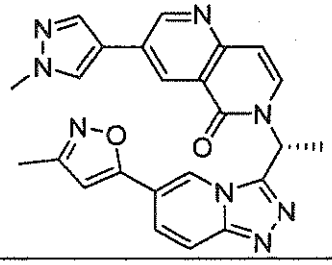
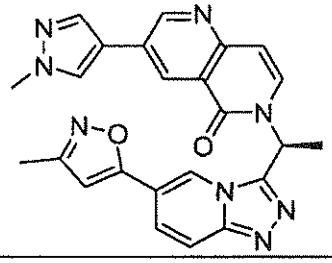
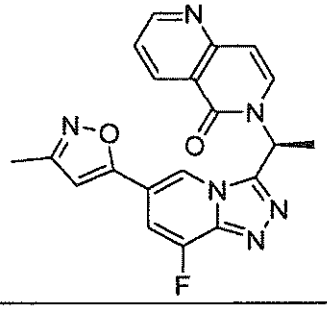
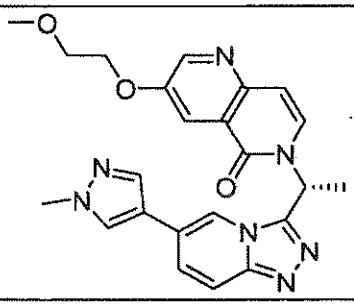
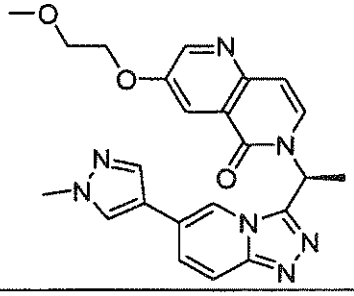
Ex	Structure	MW	Mass Found	General Method
503		389.4	390.2	N
504		389.4	390.2	N
505		420.8	420.8	N
506		420.8	420.8	N
507		389.4	389.8	N

Ex	Structure	MW	Mass Found	General Method
508		389.4	389.8	N
509		419.4	420.2	N
510		419.4	420.2	N
511		405.5	406.0	N
512		405.5	406.0	N
513		407.4	408.2	N

Ex	Structure	MW	Mass Found	General Method
514		464.5	465.2	N
515		464.5	465.2	N
516		463.2	464.2	N
517		463.2	464.2	N
518		446.5	447.2	N

Ex	Structure	MW	Mass Found	General Method
519		446.5	447.2	N
520		450.8	450.8	N
521		450.8	450.8	N
522		419.4	419.8	N
523		419.4	419.8	N

Ex	Structure	MW	Mass Found	General Method
524		420.4	420.8	N
525		420.4	420.8	N
526		488.4	488.8	N
527		470.2	471.2	N
528		470.2	471.2	N

Ex	Structure	MW	Mass Found	General Method
529		390.1	391.2	O
530		452.5	453.0	N
531		452.5	453.0	N
532		390.1	391.2	N
533		445.2	446.2	N
534		445.2	446.2	N

Example	1H NMR Data
348	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (d, *J*=2.74 Hz, 1 H), 8.53 (s, 1 H), 8.50 (d, *J*=5.28 Hz, 1 H), 8.35 (d, *J*=9.68 Hz, 1 H), 8.21 (d, *J*=0.78 Hz, 1 H), 8.17 (s, 1 H), 7.94 (d, *J*=2.64 Hz, 1 H), 7.69 - 7.73 (m, 1 H), 6.94 (d, *J*=5.38 Hz, 1 H), 5.15 (d, *J*=6.16 Hz, 2 H), 3.94 (s, 3 H)
351	1H NMR (400 MHz, CHLOROFORM-*d*) d ppm 8.66 (d, *J*=1.56 Hz, 1 H), 8.08 (d, *J*=8.51 Hz, 1 H), 7.83 - 7.93 (m, 2 H), 7.61 (s, 1 H), 7.53 (d, *J*=8.61 Hz, 1 H), 7.42 (d, *J*=9.78 Hz, 1 H), 7.33 (s, 1 H), 6.80 - 6.95 (m, 3 H), 4.78 (s, 2 H), 3.93 (s, 3 H).
352	1H NMR (400 MHz, CHLOROFORM-*d*) d ppm 8.67 (d, *J*=2.84 Hz, 1 H), 8.15 (d, *J*=8.51 Hz, 1 H), 7.94 - 7.99 (m, 1 H), 7.86 (dd, *J*=9.59 Hz, 1 H), 7.62 (s, 1 H), 7.56 (dd, *J*=8.61 Hz, 1 H), 7.34 - 7.43 (m, 2 H), 7.07 (s, 1 H), 4.77 (s, 2 H), 3.95 (s, 3 H), 2.51 (s, 3 H).
355	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3 H) 5.19 (d, *J*=6.26 Hz, 2 H) 6.95 (d, *J*=5.38 Hz, 1 H) 7.71 (dd, *J*=8.51, 4.11 Hz, 1 H) 7.94 (d, *J*=9.78 Hz, 1 H) 8.04 (t, *J*=6.21 Hz, 1 H) 8.09 (s, 1 H) 8.21 (dd, *J*=8.51, 1.56 Hz, 1 H) 8.50 (d, *J*=5.28 Hz, 1 H) 8.54 (d, *J*=9.78 Hz, 1 H) 8.79 (dd, *J*=4.11, 1.56 Hz, 1 H).
359	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (s, 3 H) 5.19 (d, *J*=6.06 Hz, 2 H) 6.96 (d, *J*=5.48 Hz, 1 H) 7.94 (d, *J*=9.68 Hz, 1 H) 8.05 (dd, *J*=10.03, 2.49 Hz, 1 H) 8.09 (s, 1 H) 8.22 (s, 1 H) 8.48 - 8.59 (m, 2 H) 8.85 (d, *J*=2.64 Hz, 1 H)
364	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (s, 3 H) 5.17 (d, *J*=6.16 Hz, 2 H) 6.94 (d, *J*=5.38 Hz, 1 H) 7.53 (t, *J*=73.21 Hz, 1 H) 7.89 - 7.99 (m, 2 H) 8.09 (s, 1 H) 8.12 (t, *J*=6.26 Hz, 1 H) 8.51 (d, *J*=5.28 Hz, 1 H) 8.54 (d, *J*=9.68 Hz, 1 H) 8.70 (d, *J*=2.74 Hz, 1 H).
365	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3 H) 3.33 (s, 3 H) 3.71 - 3.76 (m, 2 H) 4.27 - 4.31 (m, 2 H) 5.14 (d, *J*=6.16 Hz, 2 H) 6.82 (d, *J*=5.38 Hz, 1 H) 7.59 (d, *J*=2.74 Hz, 1 H) 7.94 (d, *J*=9.78 Hz, 2 H) 8.09 (s, 1 H) 8.41 (d, *J*=5.28 Hz, 1 H) 8.49 - 8.57 (m, 2 H)
370	1H NMR (400 MHz, MeOH) δ ppm 3.44 (s, 3 H) 3.82 - 3.87 (m, 2 H) 4.29 - 4.34 (m, 2 H) 5.40 (s, 2 H) 7.02 (d, *J*=5.97 Hz, 1 H) 7.19 - 7.27 (m, 1 H) 7.51 (d, *J*=2.64 Hz, 1 H) 7.75 - 7.86 (m, 2 H) 7.95 (d, *J*=9.88 Hz, 1 H) 8.33 (d, *J*=9.88 Hz, 1 H) 8.39 (d, *J*=6.26 Hz, 1 H) 8.59 (s, 1 H)
371	1H NMR (400 MHz, DMSO-d_6) δ ppm 5.02 (q, *J*=8.80 Hz, 2 H) 5.22 (d, *J*=6.26 Hz, 2 H) 6.91 (d, *J*=5.48 Hz, 1 H) 7.53 (t, *J*=9.15 Hz, 1 H) 7.79 (d, *J*=2.64 Hz, 1 H) 7.99 - 8.10 (m, 3 H) 8.21 (t, *J*=5.97 Hz, 1 H) 8.44 (d, *J*=5.28 Hz, 1 H) 8.51 (d, *J*=9.78 Hz, 1 H) 8.61 (d, *J*=2.64 Hz, 1 H)
372	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3 H) 5.02 (q, *J*=8.90 Hz, 2 H) 5.15 (d, *J*=6.16 Hz, 2 H) 6.87 (d, *J*=5.38 Hz, 1 H) 7.80 (d, *J*=2.84 Hz, 1 H) 7.94 (d, *J*=9.78 Hz, 1 H) 8.01 (t, *J*=6.11 Hz, 1 H) 8.09 (s, 1 H) 8.45 (d, *J*=5.28 Hz, 1 H) 8.54 (d, *J*=9.78 Hz, 1 H) 8.62 (d, *J*=2.84 Hz, 1 H).

Example	1H NMR Data
383	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (s, 3 H) 4.50 - 4.62 (m, 2 H) 5.14 (d, *J*=6.16 Hz, 2 H) 6.30 - 6.64 (m, 1 H) 6.87 (d, *J*=5.48 Hz, 1 H) 7.66 - 7.74 (m, 2 H) 8.06 (t, *J*=6.11 Hz, 1 H) 8.21 (d, *J*=0.68 Hz, 1 H) 8.34 (d, *J*=9.68 Hz, 1 H) 8.44 (d, *J*=5.38 Hz, 1 H) 8.52 (s, 1 H) 8.59 (d, *J*=2.84 Hz, 1 H).
390	(400 MHz, DMSO-*d6)* δ ppm 8.64 (s, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.35 (d, J = 9.6 Hz, 1Hz), 8.19 (s, 1H), 7.99 (t, J = 6.0 Hz, 1H), 7.72 (d, J = 10 Hz, 1H), 7.57 (d J = 2.8 Hz, 1H), 6.83 (d, J = 5.2 Hz, 1H), 5.12 (d, J = 6.0 Hz, 2H), 3.93 (s, 3H), 3.80-3.86 (m, 1H), 1.10-1015 (m, 2H), 1.00-1.08 (m, 2H).
399	1H NMR (400 MHz, DMSO-d_6) d ppm 8.49 - 8.55 (m, 2 H), 8.41 (d, *J*=5.38 Hz, 1 H), 8.24 (s, 1 H), 8.03 (d, *J*=9.68 Hz, 1 H), 7.94 (t, *J*=6.16 Hz, 1 H), 7.58 (d, *J*=2.84 Hz, 1 H), 6.83 (d, *J*=5.38 Hz, 1 H), 5.67 (t, *J*=5.77 Hz, 1 H), 5.15 (d, *J*=6.16 Hz, 2 H), 4.63 (d, *J*=5.67 Hz, 2 H), 3.93 (s, 3 H).
400	1H NMR (400 MHz, DMSO-d_6) δ ppm 5.26 (d, *J*=6.36 Hz, 2 H) 7.02 (d, *J*=5.38 Hz, 1 H) 7.96 - 8.10 (m, 2 H) 8.22 - 8.32 (m, 2 H) 8.48 - 8.57 (m, 3 H) 8.85 (d, *J*=2.84 Hz, 1 H)
405	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.43 - 3.53 (m, 4 H) 3.70 - 3.80 (m, 4 H) 3.94 (s, 3 H) 5.16 (d, *J*=6.16 Hz, 2 H) 6.85 (d, *J*=5.28 Hz, 1 H) 7.57 (d, *J*=2.74 Hz, 1 H) 7.87 (s, 1 H) 7.90 (d, *J*=9.68 Hz, 1 H) 8.01 - 8.08 (m, 1 H) 8.35 - 8.45 (m, 2 H) 8.52 (d, *J*=2.64 Hz, 1 H)
406	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (s, 3 H) 5.19 (d, *J*=6.26 Hz, 2 H) 6.85 (d, *J*=5.38 Hz, 1 H) 7.57 (d, *J*=2.93 Hz, 1 H) 7.97 - 8.02 (m, 1 H) 8.05 (d, *J*=9.78 Hz, 1 H) 8.42 (d, *J*=5.28 Hz, 1 H) 8.45 (d, *J*=9.68 Hz, 1 H) 8.52 (d, *J*=2.84 Hz, 1 H) 8.71 (d, *J*=1.96 Hz, 1 H) 9.36 (d, *J*=1.96 Hz, 1 H)
408	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.90 (d, *J*=7.04 Hz, 3 H) 2.44 (s, 3 H) 5.24 (q, *J*=7.01 Hz, 1 H) 7.51 (dd, *J*=8.27, 4.16 Hz, 1 H) 7.64 - 7.73 (m, 2 H) 7.81 (dd, *J*=8.75, 2.01 Hz, 1 H) 7.94 (d, *J*=1.96 Hz, 1 H) 8.00 (d, *J*=8.61 Hz, 1 H) 8.32 (d, *J*=8.41 Hz, 1 H) 8.64 (d, *J*=1.17 Hz, 1 H) 8.86 (dd, *J*=4.16, 1.71 Hz, 1 H)
409	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.92 (d, *J*=7.14 Hz, 3 H) 5.26 (q, 1 H) 7.31 (t, *J*=9.29 Hz, 1 H) 7.49 (dd, *J*=8.36, 4.16 Hz, 2 H) 7.55 (d, *J*=8.61 Hz, 1 H) 7.77 - 7.86 (m, *J*=8.22 Hz, 2 H) 7.95 (s, 1 H) 7.99 (d, *J*=8.71 Hz, 1 H) 8.31 (d, *J*=7.24 Hz, 1 H) 8.68 (s, 1 H) 8.85 (dd, *J*=4.11, 1.66 Hz, 1 H)
411	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 (d, *J*=7.04 Hz, 3 H) 2.27 (s, 3 H) 3.88 (s, 3 H) 5.22 (q, *J*=6.98 Hz, 1 H) 6.99 (s, 1 H) 7.63 (dd, *J*=8.71, 2.05 Hz, 1 H) 7.67 - 7.70 (m, 1 H) 7.72 (d, *J*=1.86 Hz, 1 H) 7.76 (dd, *J*=11.54, 1.17 Hz, 1 H) 7.93 (d, *J*=8.61 Hz, 1 H) 8.58 (d, *J*=2.93 Hz, 1 H) 8.64 (d, *J*=1.08 Hz, 1 H)
413	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3 H) 2.44 (d, *J*=23.28 Hz, 3 H) 7.56 - 7.61 (m, 2 H) 7.75 (dd, *J*=8.90, 2.15 Hz, 1 H) 7.80 (dd, *J*=11.49, 1.22 Hz, 1 H) 8.02 (d, *J*=0.88 Hz, 1 H) 8.09 (d, *J*=8.90 Hz, 1 H) 8.12 (d, *J*=2.05 Hz, 1 H) 8.43 - 8.47 (m, 1 H) 8.95 (dd, *J*=4.21, 1.76 Hz, 1 H)

Example	1H NMR Data
418	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (s, 3 H) 4.88 (s, 2 H) 7.61 (dd, *J*=8.56, 2.01 Hz, 1 H) 7.68 (d, *J*=2.74 Hz, 1 H) 7.70 - 7.75 (m, 1 H) 7.83 (s, 1 H) 7.89 (dd, *J*=11.44, 1.08 Hz, 1 H) 7.93 (d, *J*=8.61 Hz, 1 H) 8.59 (d, *J*=2.84 Hz, 1 H) 9.17 (d, *J*=1.08 Hz, 1 H)
430	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (dd, *J*=4.25, 1.71 Hz, 1 H), 8.42 - 8.46 (m, 1 H), 8.26 (d, *J*=2.05 Hz, 1 H), 8.15 (d, *J*=9.49 Hz, 1 H), 7.94 (s, 1 H), 7.90 (d, *J*=8.80 Hz, 1 H), 7.67 - 7.76 (m, 4 H), 7.52 (dd, *J*=8.26, 4.25 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.32 - 7.37 (m, 2 H), 6.17 (s, 1 H), 2.17 (s, 3 H)
431	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.85 (dd, *J*=4.21, 1.76 Hz, 1 H), 8.31 - 8.35 (m, 1 H), 8.21 (d, *J*=9.59 Hz, 1 H), 8.04 - 8.08 (m, 2 H), 7.95 - 7.99 (m, 2 H), 7.75 - 7.83 (m, 3 H), 7.49 - 7.58 (m, 4 H), 4.62 (s, 2 H)
433	1H NMR (400 MHz, DMSO-d_6) δ ppm 9.01 (dd, *J*=4.21, 1.66 Hz, 1 H), 8.54 - 8.59 (m, 1 H), 8.47 (s, 1 H), 8.44 (d, *J*=9.59 Hz, 1 H), 8.16 (d, *J*=8.80 Hz, 1 H), 8.13 (s, 1 H), 8.00 (dd, *J*=8.90, 2.05 Hz, 1 H), 7.88 (d, *J*=9.59 Hz, 1 H), 7.64 (dd, *J*=8.31, 4.21 Hz, 1 H), 7.11 (s, 1 H), 2.33 (s, 3 H)
436	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 (d, *J*=2.74 Hz, 1 H), 8.38 (d, *J*=5.38 Hz, 1 H), 8.29 (d, *J*=9.39 Hz, 1 H), 8.00 (s, 1 H), 7.76 - 7.82 (m, 3 H), 7.54 (d, *J*=2.84 Hz, 1 H), 6.79 (d, *J*=5.38 Hz, 1 H), 4.98 (d, *J*=6.36 Hz, 2 H), 3.91 (s, 3 H)
437	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.80 (s, 2 H) 7.19 (dd, *J*=10.76, 1.17 Hz, 1 H) 7.31 - 7.35 (m, 2 H) 7.38 - 7.43 (m, 4 H) 7.65 - 7.71 (m, 3 H) 8.07 (dd, *J*=8.31, 0.88 Hz, 1 H) 8.11 (d, *J*=8.41 Hz, 1 H) 8.91 (dd, *J*=4.21, 1.66 Hz, 1 H).
438	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.88 (s, 3 H) 4.76 (s, 2 H) 7.52 - 7.59 (m, 1 H) 7.61 (s, 1 H) 7.65 (d, J=12.32 Hz, 1 H) 7.80 (s, 1 H) 7.91 (d, J=8.80 Hz, 1 H) 8.01 (s, 1 H) 8.27 (s, 1 H) 8.57 - 8.66 (m, 2 H) 10.59 (br. s., 1 H)
439	1H NMR (400 MHz, DMF) δ ppm 7.69 (tt, *J*=9.32, 2.27 Hz, 3 H) 7.99 (dd, *J*=8.31, 4.21 Hz, 1 H) 8.01 - 8.09 (m, 2 H) 8.43 (dd, *J*=8.90, 2.15 Hz, 1 H) 8.54 (d, *J* = 8.8 Hz 1 H) 8.83 - 8.95 (m, 2 H) 9.19 (d, *J*=2.25 Hz, 1 H) 9.37 (dd, *J*=4.25, 1.71 Hz, 1 H) 9.53 (d, *J*=2.25 Hz, 1 H). MS m/z = 410.0 $[M+1]^+$ Calc'd for $C_{22}H_{11}F_4N_3O$: 409.3.
442	1H NMR (400 MHz, DMSO-d_6) δ ppm 4.00 (s, 3 H) 5.24 (d, *J*=5.97 Hz, 2 H) 5.76 (d, *J*=46.46 Hz, 2 H) 7.64 (d, *J*=2.74 Hz, 1 H) 7.77 (s, 1 H) 8.01 (d, *J*=9.68 Hz, 1 H) 8.10 (t, *J*=6.26 Hz, 1 H) 8.48 (d, *J*=5.28 Hz, 1 H) 8.59 (d, *J*=2.74 Hz, 1 H) 8.64 (d, *J*=9.68 Hz, 1 H).
443	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 - 2.40 (m, 1 H) 7.58 (dd, *J*=8.31, 4.21 Hz, 1 H) 7.81 (s, 1 H) 8.00 (dd, *J*=8.90, 2.25 Hz, 1 H) 8.12 (d, *J*=8.90 Hz, 1 H) 8.44 (d, *J*=1.27 Hz, 1 H) 8.47 (dd, *J*=8.46, 1.03 Hz, 1 H) 8.70 (d, *J*=2.25 Hz, 1 H) 8.95 (dd, *J*=4.26, 1.71 Hz, 1 H) 9.07 (d, *J*=2.15 Hz, 1 H) .
444	1H NMR (400 MHz, DMSO-d_6) δ ppm 7.44 - 7.53 (m, 1 H) 7.68 (dd, *J*=8.31, 4.21 Hz, 1 H) 8.00 (td, *J*=7.78, 1.76 Hz, 1 H) 8.11 (dd, *J*=8.90, 2.05 Hz, 1 H) 8.25 (dd, *J*=15.60, 8.36 Hz, 2 H) 8.55 (s, 1 H) 8.58 (dd, *J*=8.41, 0.78 Hz, 1 H) 8.75 (dq, *J*=4.77, 0.82 Hz, 1 H) 9.01 - 9.11 (m, 2 H) 9.53 (d, *J*=2.15 Hz, 1 H).

Example	1H NMR Data
450	1H NMR (400 MHz, DMSO-d_6) δ ppm 7.35 - 7.45 (m, 1 H) 7.67 (dd, *J*=8.31, 4.21 Hz, 1 H) 7.73 - 7.85 (m, 2 H) 8.11 (dd, *J*= 8.9, 2.0 Hz, 1 H) 8.21 (d, *J*=8.90 Hz, 1 H) 8.48 (d, *J*=9.10 Hz, 1 H) 8.57 (s, 1 H) 8.60 (m, 2 H) 9.04 (dd, *J*=4.11, 1.56 Hz, 1 H).
460	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (s, 3H); 3.89 (s, 3 H); 4.01 - 4.02 (m, 1 H); 7.86 (dd, *J*=8.8, 2.2 Hz, 1 H); 7.91 (dd, *J*=12.0, 1.0 Hz, 1 H); 7.95 (d, *J*=2.7 Hz, 1 H); 8.11 (d, *J*=0.7 Hz, 1 H); 8.15 (d, *J*=8.7 Hz, 1 H); 8.32 (d, *J*=1.5 Hz, 1 H); 8.56 (d, *J*=0.7 Hz, 1 H); 8.78 (d, *J*=2.9 Hz, 1 H)
462	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 - 2.07 (m, 2 H) 2.30 - 2.42 (m, 4 H) 2.43 - 2.49 (m, 2 H) 3.50 - 3.65 (m, 4 H) 3.89 (s, 3 H) 4.20 (t, *J*=6.41 Hz, 2 H) 7.86 (dd, *J*=8.75, 1.91 Hz, 1 H) 7.96 (s, 1 H) 7.98 (d, *J*=2.64 Hz, 1 H) 8.13 (s, 1 H) 8.15 (d, *J*=8.90 Hz, 1 H) 8.32 (s, 1 H) 8.46 (s, 1 H) 8.57 (s, 1 H) 8.78 (d, *J*=2.84 Hz, 1 H)
468	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.41 (s, 3 H); 3.97 (s, 3 H); 6.54 (s, 1 H); 7.39 (dd, *J*=9.8, 1.2 Hz, 1 H); 7.47 (d, *J*=2.8 Hz, 1 H); 7.83 (dd, *J*=8.8, 2.1 Hz, 1 H); 8.17 (d, *J*=1.1 Hz, 1 H); 8.21 (d, *J*=8.7 Hz, 1 H) 8.75 - 8.84 (m, 2 H)
469	1H NMR (400 MHz, DMSO-d_6) □ ppm 3.95 (s, 3 H); 7.83 - 7.92 (m, 2 H); 7.93 - 8.03 (m, 2 H); 8.18 (d, *J*=5.6 Hz, 1 H); 8.34 (s, 1 H); 8.69 (s, 1 H); 8.80 (d, *J*=2.93 Hz, 1 H)
470	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H); 7.26 (s, 1 H); 7.69 (dd, *J*=8.3, 4.2 Hz, 1 H); 8.05 (dd, *J*=8.8, 2.2 Hz, 1 H); 8.09 (dd, *J*=11.3, 1.1 Hz, 1 H); 8.25 (d, *J*=8.9 Hz, 1 H); 8.50 (d, *J*=1.7 Hz, 1 H); 8.60 (s, 1 H); 8.80 (d, *J*=1.0 Hz, 1 H); 9.08 (dd, *J*=4.3, 1.7 Hz, 1 H)
471	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.70 (s, 3 H); 7.57 - 7.67 (m, 1 H); 7.72 (s, 1 H); 7.87 - 8.16 (m, 3 H); 8.29 (s, 1 H); 8.55 (s, 1 H); 8.70 (s, 1 H)
473	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 3 H); 3.47 (s, 1 H); 3.55 (dd, *J*=11.4, 2.01 Hz, 1 H); 3.67 (s, 2 H); 3.80 (s, 1 H); 3.89 (s, 1 H); 3.98 (s, 1 H); 4.16 (d, *J*=5.0 Hz, 2 H); 7.22 (s, 1 H); 7.87 (dd, *J*=8.9, 2.0 Hz, 1 H); 7.98 (d, *J*=2.8 Hz, 1 H); 8.05 (dd, *J*=11.3, 0.6 Hz, 1 H); 8.16 (d, *J*=8.8 Hz, 1 H); 8.31 (s, 1 H); 8.74 (s, 1 H); 8.81 (d, *J*=2.9 Hz, 1 H)
474	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.35 (s, 3 H); 3.94 (s, 3 H); 4.79 (d, *J*=5.97 Hz, 2 H); 6.76 (d, *J*=5.4 Hz, 1 H); 7.01 (s, 1 H); 7.57 (d, *J*=2.7 Hz, 1 H); 7.89 - 7.94 (m, 1 H); 7.93 (d, *J*=8.6 Hz, 1 H); 8.21 (d, *J*=8.6 Hz, 1 H); 8.34 (s, 1 H); 8.40 (d, *J*=5.4 Hz, 1 H); 8.51 (d, *J*=2.7 Hz, 1 H)
475	^{1}H NMR (400 MHz, DMSO-d_6) ppm 3.89 (s, 3 H) 7.68 (dd, J=8.28, 4.27 Hz, 1 H) 7.93 (d, J=12.05 Hz, 1 H) 8.04 (d, J=8.53 Hz, 1 H) 8.13 (s, 1 H) 8.23 (d, J=8.53 Hz, 1 H) 8.43 - 8.52 (m, 2 H) 8.55 - 8.63 (m, 2 H) 9.07 (d, J=4.02 Hz, 1 H).
476	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 7.56 - 7.74 (m, 2 H) 7.99 (d, J=9.03 Hz, 1 H) 8.21 (d, J=8.53 Hz, 1 H) 8.40 (s, 1 H) 8.57 (d, J=8.03 Hz, 1 H) 8.63 (d, J=10.04 Hz, 1 H) 9.05 (d, J=4.02 Hz, 1 H)
477	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 3.92 (s, 3 H) 3.94 (s, 3 H) 7.80 - 7.87 (m, 2 H) 8.01 - 8.07 (m, 1 H) 8.11 (d, J=9.04 Hz, 1 H) 8.37 (s, 1 H) 8.46 - 8.51 (m, 2 H) 8.75 (d, J=3.01 Hz, 1 H)

Example	1H NMR Data
478	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 7.67 (dd, J=8.03, 4.02 Hz, 1 H) 7.80 - 7.89 (m, 2 H) 8.17 (dd, J=13.05, 9.54 Hz, 2 H) 8.54 (s, 1 H) 8.60 (d, J=8.53 Hz, 1 H) 8.69 (d, J=10.04 Hz, 1 H) 9.04 (d, J=3.51 Hz, 1 H)
484	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 2.94 (t, J=7.78 Hz, 2 H) 3.03 - 3.14 (m, 2 H) 7.44 (d, J=8.03 Hz, 2 H) 7.68 (dd, J=8.28, 4.27 Hz, 1 H) 7.85 (br. s., 2 H) 7.95 (d, J=8.03 Hz, 2 H) 8.05 (d, J=8.53 Hz, 1 H) 8.12 (d, J=9.54 Hz, 1 H) 8.21 (d, J=8.53 Hz, 1 H) 8.49 (s, 1 H) 8.57 - 8.66 (m, 2 H) 9.05 (d, J=4.02 Hz, 1 H).
490	^{1}H NMR (300 MHz, CHLOROFORM-d) d ppm 2.10 (d, J=7.16 Hz, 3 H) 2.55 (s, 3 H) 5.04 (q, J=6.87 Hz, 1 H) 7.27 - 7.52 (m, 3 H) 7.82 (d, J=8.62 Hz, 1 H) 7.93 (s, 1 H) 8.05 (d, J=8.62 Hz, 1 H) 8.15 (d, J=9.21 Hz, 2 H) 8.85 (d, J=2.63 Hz, 1 H).
496	^{1}H NMR (300 MHz, CHLOROFORM-d)ppm 3.58 (s, 3 H) 4.78 (s, 2 H) 7.48 - 7.63 (m, 4 H) 7.66 (d, J=8.48 Hz, 1 H) 7.87 (d, J=7.16 Hz, 1 H) 7.91 - 8.06 (m, 3 H) 8.14 (d, J=9.65 Hz, 1 H) 8.47 (s, 1 H).
499	^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 3.94 (s, 3 H) 4.73 (s, 2 H) 7.10 (d, J=9.65 Hz, 1 H) 7.33 (d, J=2.78 Hz, 1 H) 7.63 (d, J=10.67 Hz, 1 H) 7.76 (s, 1 H) 8.00 (d, J=8.48 Hz, 1 H) 8.07 (d, J=9.65 Hz, 1 H) 8.64 (d, J=2.92 Hz, 1 H).
501	^{1}H NMR (300 MHz, MeOH) d ppm 4.05 (s, 11 H) 4.82 (s, 7 H) 7.40 (dd, J=10.08, 1.46 Hz, 4 H) 7.81 (dd, J=8.77, 1.90 Hz, 4 H) 7.96 (d, J=0.88 Hz, 4 H) 8.05 (d, J=8.77 Hz, 4 H) 8.21 (d, J=2.78 Hz, 4 H) 8.50 (d, J=0.73 Hz, 3 H) 8.85 (d, J=2.92 Hz, 4 H).
502	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.59 (s, 3 H) 3.93 (s, 3 H) 4.77 (s, 2 H) 7.34 (d, *J*=2.74 Hz, 1 H) 7.38 (d, *J*=9.68 Hz, 1 H) 7.46 (s, 1 H) 7.66 (dd, *J*=8.61, 2.05 Hz, 1 H) 7.84 (d, *J*=1.96 Hz, 1 H) 7.98 (d, *J*=8.61 Hz, 1 H) 8.16 (d, *J*=9.59 Hz, 1 H) 8.61 (d, *J*=2.93 Hz, 1 H).

Example	^{1}H NMR Data
503	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.16 (d, *J*=5.18 Hz, 3 H) 3.97 (s, 3 H) 6.82 (d, *J*=6.55 Hz, 1 H) 7.01 - 7.13 (m, 2 H) 7.41 - 7.49 (m, 1 H) 7.54 (d, *J*=6.26 Hz, 1 H) 7.61 (s, 1 H) 7.71 (s, 1 H) 8.33 (s, 1 H) 8.78 (d, *J*=7.73 Hz, 1 H) 8.93 (s, 1 H).
505	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 6.78 (d, *J*=7.82 Hz, 1 H) 7.03 (d, *J*=6.94 Hz, 1 H) 7.54 (dd, *J*=8.07, 4.55 Hz, 1 H) 7.78 (d, *J*=7.82 Hz, 1 H) 7.97 - 8.09 (m, 2 H) 8.16 (dd, *J*=8.56, 2.49 Hz, 1 H) 8.61 (dd, *J*=7.97, 1.71 Hz, 1 H) 8.70 - 8.78 (m, 1 H) 8.92 (dd, *J*=4.55, 1.81 Hz, 1 H) 9.03 (d, 1 H).
507	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.97 (d, *J*=6.94 Hz, 3 H) 3.68 (s, 3 H) 6.75 (d, *J*=7.73 Hz, 1 H) 6.94 (d, *J*=6.85 Hz, 1 H) 7.52 - 7.59 (m, 1 H) 7.64 (dd, *J*=7.78, 0.54 Hz, 1 H) 7.69 - 7.75 (m, 3 H) 8.46 (s, 1 H) 8.63 (dt, *J*=8.12, 0.88 Hz, 1 H) 8.90 - 8.94 (m, 1 H)
509	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 4.00 - 4.09 (m, 2 H) 4.29 - 4.33 (m, 2 H) 6.91 (d, *J*=7.92 Hz, 1 H) 7.04 (dd, 1 H) 7.10 (dd, *J*=10.56, 1.17 Hz, 1 H) 7.51 (dd, *J*=8.17, 4.74 Hz, 1 H) 7.59 (d, *J*=7.82 Hz, 1 H) 7.72 (d, *J*=0.68 Hz, 1 H) 7.76 (d, *J*=0.78 Hz, 1 H) 8.34 (d, *J*=1.17 Hz, 1 H) 8.84 (dd, *J*=8.07, 1.22 Hz, 1 H) 8.92 (dd, *J*=4.74, 1.81 Hz, 1 H)

Example	^{1}H NMR Data
514	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 2.39 (s, 3 H) 3.49 (s, 3 H) 3.78 - 3.94 (m, 2 H) 4.23 - 4.43 (m, 2 H) 6.43 (s, 1 H) 6.85 (d, *J*=7.82 Hz, 1 H) 7.08 (q, *J*=7.11 Hz, 1 H) 7.29 (dd, *J*=10.07, 1.17 Hz, 1 H) 7.43 (d, *J*=7.82 Hz, 1 H) 8.17 (d, *J*=2.93 Hz, 1 H) 8.58 - 8.81 (m, 2 H).
516	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.15 (d, *J*=7.14 Hz, 3 H) 3.49 (s, 3 H) 3.80 - 3.90 (m, 2 H) 3.97 (s, 3 H) 4.27 - 4.39 (m, 2 H) 6.83 (d, *J*=7.73 Hz, 1 H) 7.00 - 7.13 (m, 2 H) 7.42 (d, *J*=7.82 Hz, 1 H) 7.61 (s, 1 H) 7.72 (s, 1 H) 8.15 (d, *J*=2.84 Hz, 1 H) 8.31 (s, 1 H) 8.72 (d, *J*=3.03 Hz, 1 H).
518	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (t, 1 H), 8.68 (d, *J*=3.03 Hz, 1 H), 8.01 - 8.02 (m, 1 H), 7.96 (dd, *J*=9.59, 1.08 Hz, 1 H), 7.79 (dd, *J*=9.54, 1.61 Hz, 1 H), 7.60 (d, *J*=7.82 Hz, 1 H), 7.01 - 7.05 (m, 1 H), 6.99 (s, 1 H), 6.75 (d, *J*=7.63 Hz, 1 H), 4.29 - 4.32 (m, 2 H), 3.70 - 3.73 (m, 2 H), 3.32 (s, 3 H), 2.31 (s, 3 H), 1.99 (d, *J*=7.04 Hz, 3 H).
524	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.94 (s, 3 H) 6.77 (dd, *J*=7.78, 0.54 Hz, 1 H) 6.94 - 7.05 (m, 2 H) 7.64 (d, *J*=7.82 Hz, 1 H) 7.76 - 7.89 (m, 1 H) 7.98 (dd, *J*=3.08, 0.54 Hz, 1 H) 8.68 (d, *J*=3.03 Hz, 1 H) 8.80 (d, *J*=1.08 Hz, 1 H).
526	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.25 - 2.38 (m, 3 H) 5.05 (q, *J*=8.77 Hz, 2 H) 6.74 - 6.83 (m, 1 H) 6.96 - 7.07 (m, 2 H) 7.71 (d, *J*=7.82 Hz, 1 H) 7.86 (dd, *J*=11.49, 1.12 Hz, 1 H) 8.20 (d, *J*=2.74 Hz, 1 H) 8.78 (d, *J*=3.03 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H)
527	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.89 (s, 3 H) 6.78 (d, *J*=8.41 Hz, 1 H) 6.95 - 7.09 (m, 2 H) 7.72 (d, *J*=7.82 Hz, 1 H) 7.85 (d, *J*=12.62 Hz, 1 H) 8.12 (s, 1 H) 8.46 (s, 1 H) 8.67 (dd, *J*=2.35, 0.68 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H) 9.20 (d, *J*=2.45 Hz, 1 H)
529	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 6.78 (d, *J*=7.92 Hz, 1 H) 6.95 - 7.12 (m, 2 H) 7.54 (dd, *J*=8.22, 4.50 Hz, 1 H) 7.77 (d, *J*=7.73 Hz, 1 H) 7.85 (d, *J*=11.54 Hz, 1 H) 8.62 (d, *J*=9.59 Hz, 1 H) 8.82 (s, 1 H) 8.92 (dd, *J*=4.55, 1.71 Hz, 1 H)

Although the pharmacological properties of the compounds of the current invention vary with structural change, in general, activity possessed by these compounds may be demonstrated *in vivo*. The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological *in vitro* assays. The exemplified pharmacological assays, which follow, have been carried out with the compounds according to the invention. The exemplified compounds of the present invention demonstrated a K_i between 20 μM and 0.1 nM. Illustrative activity values are provided in the following table.

Ex.	cMet K_i (μM)
373	0.0001

Ex.	cMet K_i (μM)
430	0.3480
437	0.0364
439	0.2531
440	0.1716
441	0.0286
447	0.0121
450	0.1823
466	0.6351

Ex.	cMet Ki (μM)
503	0.0015
505	0.0015
508	1.3438
509	0.0032
511	0.0005
514	0.0007
516	0.0061
518	0.0015
520	0.0011
522	0.0011
524	0.0009
525	0.0257
527	0.0003
529	0.0021

BIOLOGICAL TESTING

The efficacy of the compounds of the invention as inhibitors of HGF related activity is demonstrated as follows.

c-Met receptor assay

Cloning, Expression and Purification of c-Met Kinase Domain

1) A PCR product covering residues 1058-1365 of c-Met (c-Met kinase domain) is generated from Human Liver QuickClone™ cDNA (Invitrogen) as described in WO 08/008539.

2). The PCR product is cloned into a modified pFastBac1 expression vector (harboring the gene for *S. japonicum* glutathione S-transferase immediately upstream of the multiple cloning site) using standard molecular biological techniques. The GST-c-Met kinase domain fusion (GST-Met) gene is transposed into full-length baculovirus DNA using the

BacToBac™ system (Invitrogen). High5 cells are infected with the recombinant baculovirus for 72 h at 27°C. The infected cells are harvested by centrifugation and the pellet is stored at –80°C. The pellet is resuspended in buffer A (50 mM HEPES, pH 8.0, 0.25 M NaCl, 10 mM 2-mercaptoethanol, 10% (w/v) glycerol, 0.5 % (v/v) protease inhibitor cocktail (Sigma P8340), stirred at 4°C to homogeneity, and the cells are disrupted by microfluidization (Microfluidics) at 10,000 psi. The resulting lysate is centrifuged at 50,000 x *g* for 90 min at 4 °C, and the supernatant is adsorbed onto 10 mL of glutathione sepharose™ 4B (Amersham) by batch method. The slurry is rocked gently overnight at 4°C. The glutathione resin is harvested by centrifugation and washed three times with 40 mL buffer A by batch method. The resin is washed three times with buffer B (buffer A adjusted to 0.1 M NaCl, less protease inhibitors). The protein is eluted with buffer B containing 25 mM reduced glutathione. Eluted fractions are analyzed by SDS-PAGE and concentrated to <10 mL (~10 mg/mL total protein). The concentrated protein is separated by Superdex™ 200 (Amersham) size exclusion chromatography in buffer C (25 mM Tris, pH 7.5, 0.1 M NaCl, 10 mM 2-mercaptoethanol, 10% glycerol). The fractions are analyzed by SDS-PAGE and the appropriate fractions are pooled and concentrated to ~1 mg/mL. The protein is aliquotted and stored at –80°C.

Alternative purification of human GST-cMET from Baculovirus cells

Baculovirus cells are broken in 5x (volume/weight) of Lysis Buffer (50 mM HEPES, pH 8.0, 0.25 M NaCl, 5 mM mercaptoethanol, 10% glycerol plus Complete Protease Inhibitors (Roche (#10019600), 1 tablet per 50 mL buffer). The lysed cell suspension is centrifuged at 100,000 x g (29,300 rpm) in a Beckman ultracentrifuge Ti45 rotor for 1 h. The supernatant is incubated with 10 ml of Glutathione Sepharose 4B from Amersham Biosciences (#27-4574-01). Incubation is carried out overnight in a cold room (approximately 8°C). The resin and supernatant is poured into an appropriately sized disposable column and the flow through supernatant was collected. The resin is washed with 10 column volumes (100 mL) of Lysis Buffer. The GST-cMET is eluted with 45 mL of 10 mM Glutathione (Sigma #G-4251) in Lysis Buffer. The elution is collected as 15 mL fractions. Aliquots of the elution fractions are run on SDS PAGE (12% Tris Glycine gel, Invitrogen, #EC6005BOX). The gel is stained with 0.25% Coomassie Blue stain. Fractions with GST-cMET are concentrated with a Vivaspin 20 mL Concentrator (#VS2002; 10,00 MW cutoff) to a final volume less than 2.0 ml. The concentrated GST-cMET solution is applied to a Superdex 75 16/60 column (Amersham Biosciences #17-1068-01) equilibrated with 25 mM Tris, pH 7.5, 100 mM NaCl, 10 mM mercaptoethanol, 10% glycerol. The GST-cMET is eluted with an isocratic run of the above buffer, with the eluent collected in 1.0 mL fractions. Fractions with significant OD_{280} readings

are run on another 12% Tris Glycine gel. The peak tubes with GST-cMET are pooled and the OD_{280} is read with the column buffer listed above as the blank buffer.

Phosphorylation of the purified GST-cMET is performed by incubating the protein for 3 h at RT with the following:

	Final concentration
a) 100 mM ATP (Sigma #A7699)	25 mM
b) 1.0 M $MgCl_2$ (Sigma #M-0250)	100 mM
c) 200 mM Sodium Orthovanadate (Sigma #S-6508)	15 mM
d) 1.0 M Tris-HCl, pH 7.00 (in house)	50 mM
e) H_20	
f) GST-cMET	0.2 - 0.5 mg/mL

After incubation, the solution is concentrated in a Vivaspin 20 ml Concentrator to a volume less than 2.00 ml. The solution is applied to the same Superdex 75 16/60 column used above after re-equilibration. The GST-cMET is eluted as described above. The elution fractions corresponding to the first eluted peak on the chromatogram are run on a 12% Tris Glycine gel, as above, to identify the fractions with GST-cMET. Fractions are pooled and the OD_{280} is read with the column buffer used as the blank.

A Kinase reaction Buffer is prepared as follows:

			Per 1 L
60 mM HEPES pH 7.4	1 M stock	16.7 X	60 mL
50 mM NaCl	5 M stock	100 X	10 mL
20 mM $MgCl_2$	1 M stock	50 X	20 mL
5 mM $MnCl_2$	1 M stock	200 X	5 mL

When the assay is carried out, freshly add:

2 mM DTT	1 M stock	500 X
0.05 % BSA	5 % stock	100 X
0.1 mM Na_3OV_4	0.1 M stock	1000 X

The HTRF buffer contains:

50 mM Tris-HCl (pH 7.5), 100 mM NaCl, 0.1 % BSA, 0.05 % Tween 20,5mM EDTA

Fresh add SA-APC (PJ25S Phycolink Streptavidin-Allophycocyanin Conjugate, Prozyme Inc.) and Eu-PT66 (Eu-W1024 labeled anti-phosphorotyrosine antibody PT66, AD0069, Lot 168465, Perkin-Elmer Inc.) to reach the final concentration:

0.1 nM final Eu-PT66

11 nM final SA-APC

Methods:

1. Dilute GST-cMet (P) enzyme in kinase buffer as follows:

Prepare 8 nM GST-cMet (P) working solution (7.32 μM to 8 nM, 915 X, 10 μL to 9.15 mL). In a 96 well clear plate [Costar # 3365] add 100 μL in eleven columns, in one column add 100 μL kinase reaction buffer alone.

2. Assay plate preparation:

Use Biomek FX to transfer 10 μL 8 nM GST-cMet (P) enzyme, 48.4 μL kinase reaction buffer, 1.6 μL compound (in DMSO) (Start concentration at 10 mM, 1 mM and 0.1 mM, sequential dilution 1:3 to reach 10 test points) in a 96 well costar clear plate [Costar # 3365], mix several times. Then incubate the plate at RT for 30 min.

3. Prepare Gastrin and ATP working solution in kinase reaction buffer as follows:

Prepare 4 μM Gastrin and 16 μM ATP working solution

		Per 10 mL
Gastrin 4 μM stock	(500 μM to 4 μM, 125 X)	80 μL
ATP 16 μM stock	(1000 μM to 16 μM, 62.5 X)	160 μL

Use Biomek FX to add 20 μl ATP and Gastrin working solution to the assay plate to start reaction, incubate the plate at RT for 1 h.

4. Transfer 5 μL reaction product at the end of 1 h into 80 μL HTRF buffer in black plate [Costar # 3356], read on Discover after 30 min incubation.

Assay condition summary:

K_M ATP *	-	6 μM
[ATP]	-	4 μM
K_M Gastrin/p(EY)	-	3.8 μM

[gastrin] - 1 μM

[enzyme] - 1 nM

K_M ATP, K_M gastrin for various enzymes were determined by HTRF/^{33}P labeling and HTRF methods.

Examples 1-28, 30, 33-34, 36-37, and 39-48 exhibited activity with IC_{50} values less than 0.5 μM.

c-Met cell-based autophosphorylation assay

Human PC3 and mouse CT26 cells are available obtained from ATCC. The cells were cultured in a growth medium containing RPMI 1640, penicillin/streptomycin/glutamine (1X) and 5% FBS. 2 x 10^4 cells in medium were plated per well in a 96 well plate and incubated at 37 °C overnight. The cells were serum-starved by replacing the growth media with basic medium (DMEM low glucose + 0.1 BSA, 120 μL per well) at 37 °C for 16 h. Compounds (either 1 mM and 0.2 mM) in 100% DMSO were serially diluted (1:3) 3333 fold on a 96 well plate, diluting 1:3 with DMSO from column 1 to 11 (columns 6 and 12 receive no compound). Compound samples (2.4 μL per well) were diluted with basic medium (240 μL) in a 96 well plate. The cells were washed once with basic medium (GIBCO, DMEM 11885-076) then compound solution was added (100 μL). The cells were incubated at 37 °C for 1 h. A (2 mg/mL) solution of CHO-HGF (7.5 μL) was diluted with 30 mL basic medium to provide a final concentration of 500 ng/mL. This HGF-containing media (120 μL) was transferred to a 96 well plate. Compounds (1.2 μL) was added to the HGF-containing media and mixed well. The mixture of media/HGF/compound (100 μL) was added to the cells (final HGF concentration - 250 ng/mL) then incubated at 37 °C for 10 min. A cell lysate buffer (20 mL) was prepared containing 1% Triton X-100, 50 mM Tris pH 8.0, 100 mM NaCl, Protease inhibitor (Sigma, #P-8340) 200 μL, Roche Protease inhibitor (Complete, # 1-697-498) 2 tablets, Phosphatase Inhibitor II (Sigma, #P-5726) 200 μL, and a sodium vanadate solution (containing 900 μL PBS, 100 μL 300 mM $NaVO_3$, 6 μL H_2O_2 (30% stock) and stirred at RT for 15 min) (90 μL). The cells were washed once with ice cold 1X PBS (GIBCO, #14190-136), then lysis buffer (60 μL) was added and the cells were incubated on ice for 20 min.

The IGEN assay was performed as follows: Dynabeads M-280 streptavidin beads were pre-incubated with biotinylated anti-human HGFR (240 μL anti-human-HGFR (R&D system, BAF527 or BAF328) @ 100 μg/mL + 360 μL Beads (IGEN #10029 + 5.4 μL buffer – PBS/1% BSA/0.1% Tween20) by rotating for 30 min at RT. Antibody beads (25 μL) were transferred to a 96 well plate. Cell lysate solution (25 μL) was transferred added and the plate was shaken

at RT for 1 h. Anti-phosphotyrosine 4G10 (Upstate 05-321) (19.7 μL antibody + 6 mL 1X PBS) (12.5 μL) was added to each well, then incubated for 1 h at RT. Anti-mouse IgG ORI-Tag (ORIGEN #110087) (24 μL Antibody + 6 mL buffer) (12.5 μL) was added to each well, then incubated at RT for 30 min. 1X PBS (175 μL) was added to each well and the electrochemiluminescence was read by an IGEN M8. Raw data was analyzed using a 4-parameter fit equation in XLFit. IC_{50} values are then determined using Grafit software. Examples 2, 4, 6-8, 11, 13, 15-21, 23-26, 36-37, 39, 41, and 43-44 exhibited activity in PC3 cells with IC_{50} values less than 1.0 μM. Examples 2, 4, 6-8, 11-13, 15-21, 23-26, 36-37, 41, and 43-44 exhibited activity in CT26 cells with IC_{50} values less than 1.0 μM.

rHu-bFGF: Stock concentration of 180 ng/μL: R&D rHu- bFGF: Added 139 μL of the appropriate vehicle above to the 25 μg vial lyophilized vial. 13.3 μL of the [180 ng/μL] stock vial and added 26.6 μL of vehicle to yield a final concentration of 3.75 μM concentration.

Nitro-cellulose disk preparation: The tip of a 20-gauge needle was cut off square and beveled with emery paper to create a punch. This tip was then used to cut out ≅ 0.5 mm diameter disks from a nitrocellulose filter paper sheet (Gelman Sciences). Prepared disks were then placed into Eppendorf microfuge tubes containing solutions of either 0.1% BSA in PBS vehicle, 10 μM rHu-VEGF (R&D Systems, Minneapolis, MN), or 3.75 μM rHu-bFGF (R&D Systems, Minneapolis, MN) and allowed to soak for 45-60 min before use. Each nitrocellulose filter disk absorbs approximately 0.1 μL of solution.

In the rat micropocket assay, compounds of the present invention will inhibit angiogenesis at a dose of less than 50 mg/kg/day.

Tumor model

A431 cells (ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n = 5-15). Subsequent administration of compound by oral gavage (10 - 200 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (Ora-Plus, pH 2.0) is the negative control. Compounds of the present invention will be active at doses less than 150 mpk.

Tumor models

Human glioma tumor cells (U87MG cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control. Compounds of the present invention will be active at 150 mpk.

Human gastric adenocarcinoma tumor cells (MKN45 cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control. Compounds of the present invention will be active at 150 mpk.

FORMULATIONS

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of the current invention in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, preferably between about 0.01 and about 50 mg/kg, and more preferably about 0.01 and about 30 mg/kg body weight may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg

administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound, which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a

non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are

solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes, which are obvious to one skilled in the art are intended to be within the scope and nature of the invention, which are defined, in the appended claims.

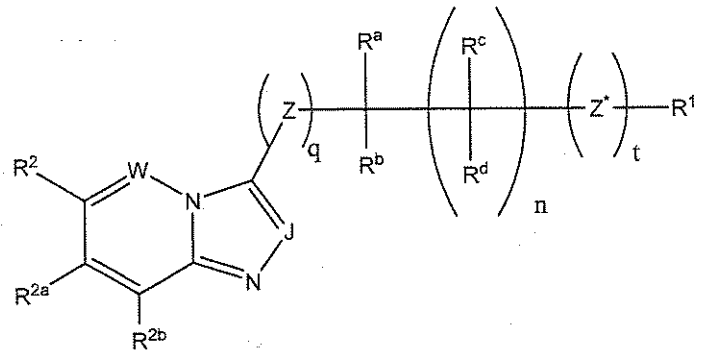
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

WE CLAIM:

1. A compound of formula I



I

wherein

J is N or CR^3;

W is CR^{2b};

Z and Z* are independently -O-, $-S(O)_v-$, or $-NR^5-$;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

R^1 is aryl, heteroaryl or heterocyclo any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^2 is

(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

R^{2a}, R^{2b} and R^3 are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} at each occurrence is independently, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

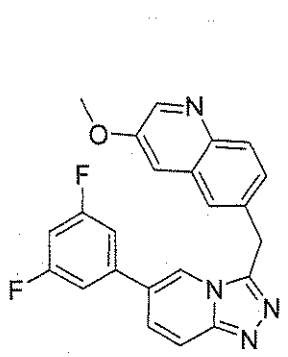
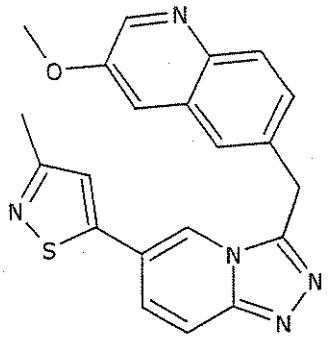
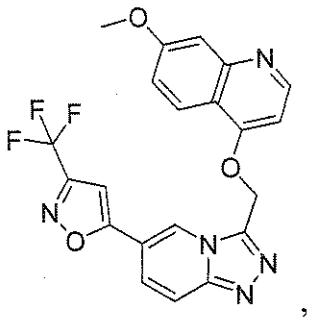
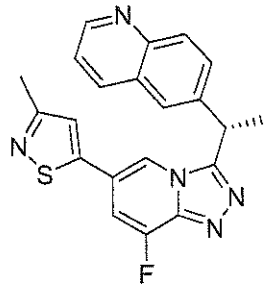
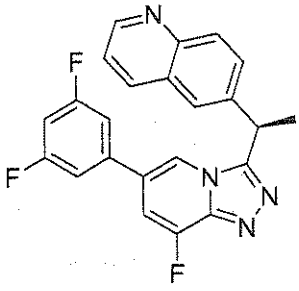
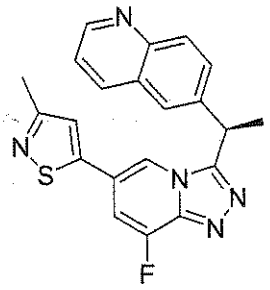
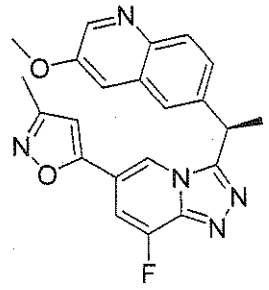
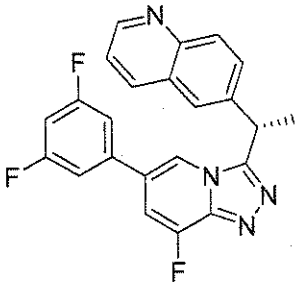
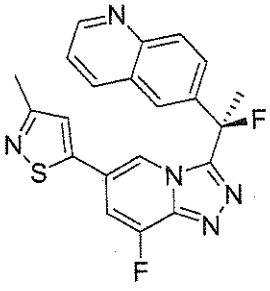
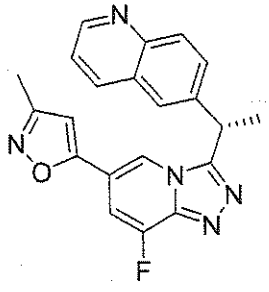
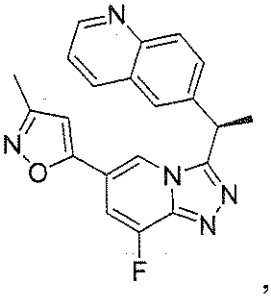
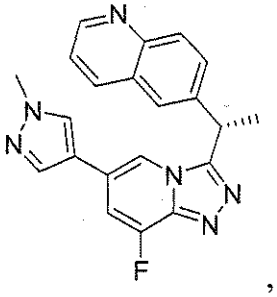
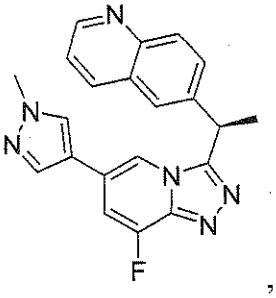
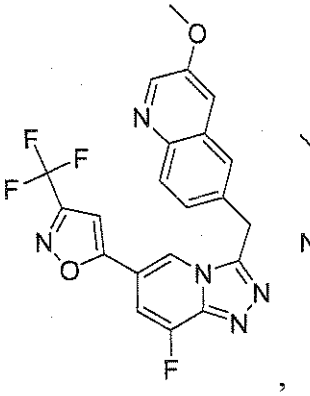
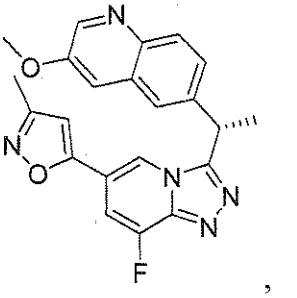
m is 0 or 1;

n is 0, 1 or 2;

q and t are each independently 0 or 1;

v is 0, 1 or 2;

wherein said compound is selected from

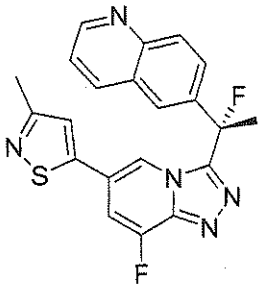
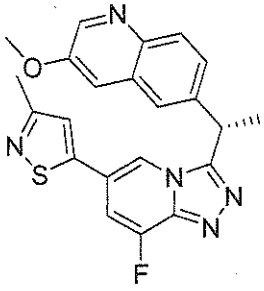
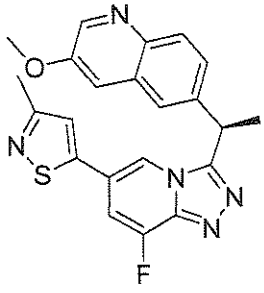
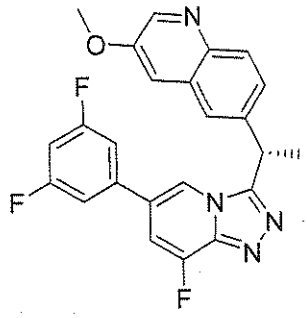
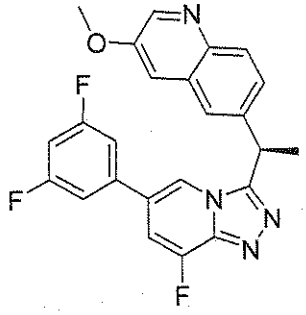
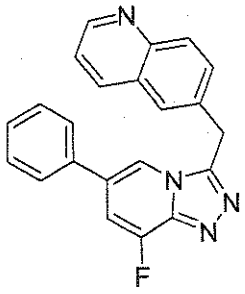
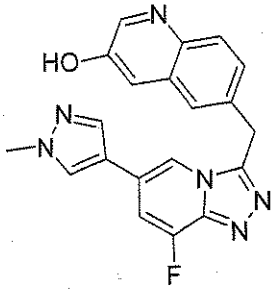
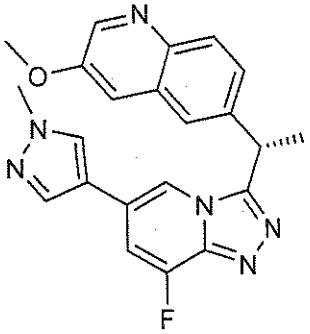
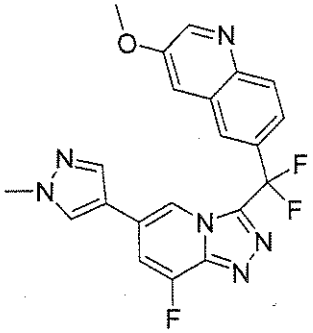
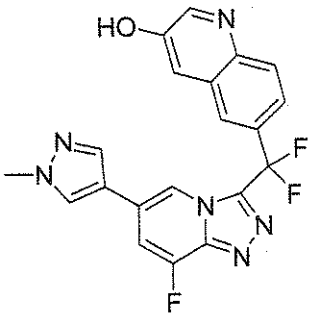
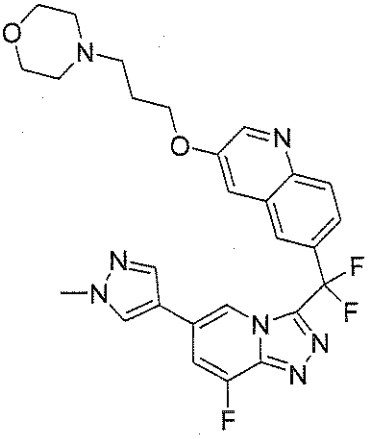
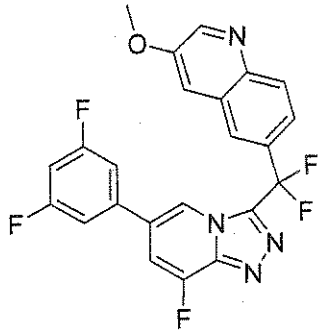
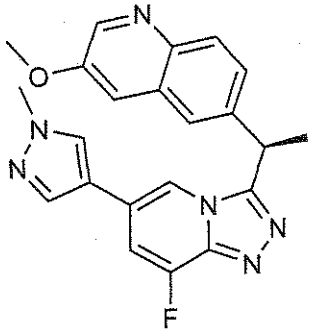
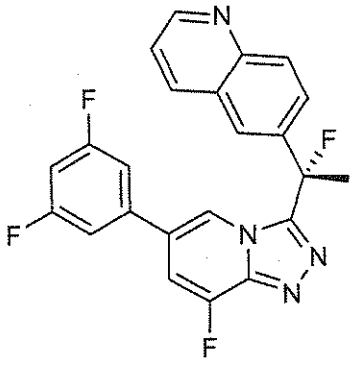

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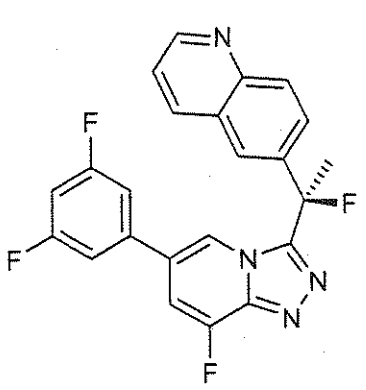
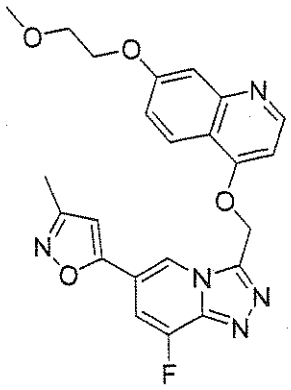
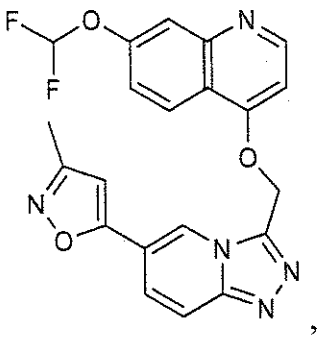
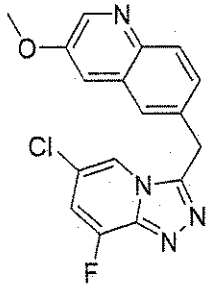
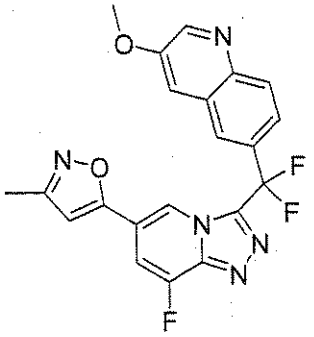
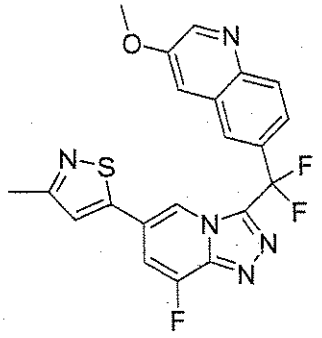
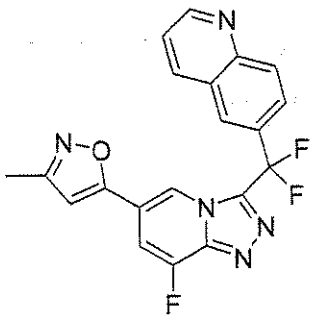
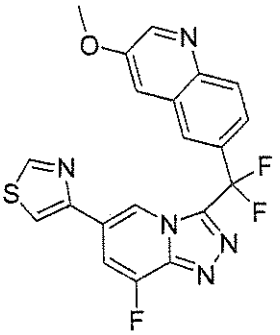
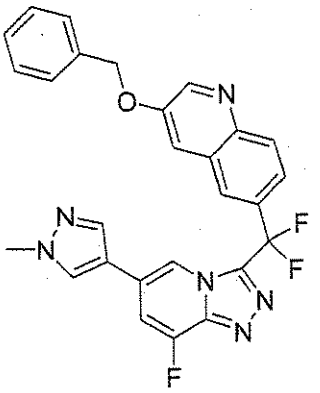
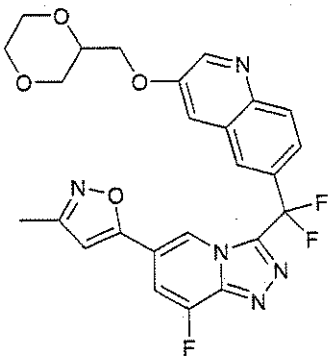
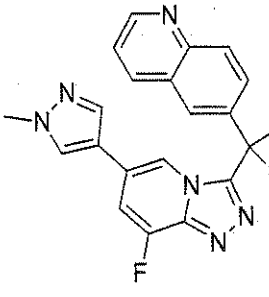
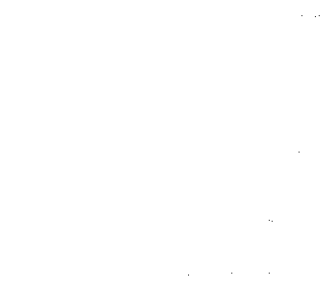
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and salts thereof.

2. A pharmaceutical composition comprising a compound of claim 1 together with a pharmaceutically acceptable vehicle or carrier.

3. A compound as claimed in either claim 1 for treating cancer in a subject.

4. Use of a compound as claimed in either claim 1 in the manufacture of a medicament for treating cancer in a subject.

5. The compound of claim 3 or use of claim 4 wherein said compound is administered in combination with at least one compound selected from antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, and interferon-type agents.

6. A compound as claimed in claim 1 for reducing tumor size in a subject.

7. Use of a compound as claimed in claim 1 in the manufacture of a medicament for reducing tumour size in a subject.

8. A compound as claimed in claim 1 for treating HGF mediated disorders in a subject.

9. Use of a compound as claimed in claim 1 in the manufacture of a medicament for treating HGF mediated disorders in a subject.

10. A compound as claimed in claim 1 for reducing metastasis in a tumor in a subject.

11. Use of a compound as claimed in claim 1 in the manufacture of a medicament for reducing metastasis in a tumor in a subject.